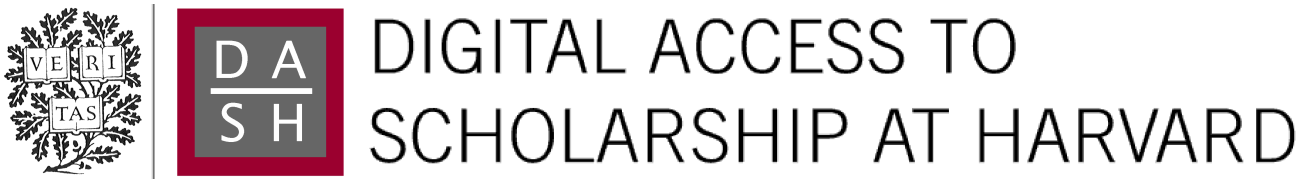

Quasi-Experimental Health Policy Research: Evaluation of Universal Health Insurance and Methods for Comparative Effectiveness Research

HARVARD UNIVERSITY
Graduate School of Arts and Sciences

DISSERTATION ACCEPTANCE CERTIFICATE

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Quasi-Experimental Health Policy Research: Evaluation of Universal Health Insurance and Methods for Comparative Effectiveness Research

presented by Laura Faden Garabedian

candidate for the degree of Doctor of Philosophy and hereby certify that it is worthy of acceptance.

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Quasi-Experimental Health Policy Research: Evaluation of Universal Health Insurance and Methods for Comparative Effectiveness Research

A dissertation presented

by

Laura Faden Garabedian

to

The Committee on Higher Degrees in Health Policy

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Professor Stephen Soumerai Laura Faden Garabedian

Quasi-Experimental Health Policy Research: Evaluation of Universal Health Insurance and Methods for Comparative Effectiveness Research

Abstract

This dissertation consists of two empirical papers and one methods paper. The first two papers use quasi-experimental methods to evaluate the impact of universal health insurance reform in Massachusetts (MA) and Thailand and the third paper evaluates the validity of a quasi-experimental method used in comparative effectiveness research (CER).

My first paper uses interrupted time series with data from IMS Health to evaluate the impact of Thailand's universal health insurance and physician payment reform on utilization of medicines for three non-communicable diseases: cancer, cardiovascular disease and diabetes. Expanding health insurance coverage with a medicines benefit to the entire Thai population increased access to medicines in primary care. But, there is evidence of potential unintended consequences of the reform - the universal coverage scheme did not increase use of medicines for diseases that are typically treated in secondary or tertiary care settings, or increase market penetration for generic drugs.

My second paper evaluates the impact of the MA health insurance reform on short-term enrollment and adverse selection in the unsubsidized individual insurance market. This project employed interrupted time series and pre-post survival analytic methods with claims data from Harvard Pilgrim Health Care (HPHC). Contrary to previous unpublished reports, we found that short-term enrollment decreased after the reform. And, post-reform members had lower rates of inpatient stays and emergency department visits, which suggests that the MA reform, as intended, actually reduced adverse selection in the overall individual market. However, there

was a post-reform increase in use of infertility treatments, which are expensive elective procedures.

My third paper evaluates the validity of instrumental variable (IV) methods in CER. We performed a systematic review of the health and economic literature to identify IVs used in CER, evaluated trends in the use of IVs in published CER studies, and identified the existence and impact of potential IV-outcome confounders for commonly used IVs. We found that IV analysis is an increasingly popular method for CER. There was overwhelming evidence of potential IV-outcome confounders of the four most popular IVs that call into question the trustworthiness of the results of IV CER studies.

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I dedicate this dissertation to Berj and our soon-to-be-born son, Thomas Arthur.

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Chapter 1: Impact of Universal Health Insurance Coverage in Thailand on Sales and Market Share of Medicines for Non-Communicable Diseases [a,b]

[a] This chapter has been published as: Garabedian LF, Ross-Degnan D, Ratanawijitrasin S, Stephens P, Wagner AK. Impact of universal health insurance coverage in Thailand on sales and market share of medicines for non-communicable diseases: an interrupted time series study. *BMJ Open*. 2012;2:e001686 doi:10.1136/bmjopen-2012-001686. Available online at: http://bmjopen.bmj.com/content/2/6/e001686.full

[b] This project received ethics approval from the Harvard Pilgrim Health Care Institute Office of Sponsored Programs.

ABSTRACT

Objective: In 2001, Thailand implemented the Universal Coverage Scheme (UCS), a public insurance system that aimed to achieve universal access to health care, including essential medicines, and to influence primary care centers and hospitals to use resources efficiently, via capitated payment for outpatient services and other payment policies for inpatient care. Our objective was to evaluate the impact of the UCS on utilization of medicines in Thailand for three non-communicable diseases: cancer, cardiovascular disease, and diabetes.

Design: Interrupted time series design, with a non-equivalent comparison group.

Setting: Thailand, 1998-2006.

Data: Quarterly purchases of medicines from hospital and retail pharmacies collected by IMS Health between 1998 and 2006.

Intervention: UCS implementation, April-October 2001.

Outcome measures: Total pharmaceutical sales volume and percent market share by licensing status and National Essential Medicine List (NEML) status.

Results: The UCS was associated with long-term increases in sales of medicines for conditions that are typically treated in outpatient primary care settings, such as diabetes, high cholesterol and high blood pressure, but not for medicines for diseases that are typically treated in secondary or tertiary care settings, such as heart failure, arrhythmias, and cancer. While the majority of increases in sales were for essential medicines, there were also post-policy increases in sales of non-essential medicines. Immediately following the reform, there was a significant shift in hospital sector market share by licensing status for most classes of medicines. Government-produced products often replaced branded generic or generic competitors.

Conclusions: Our results suggest that expanding health insurance coverage with a medicines benefit to the entire Thai population increased access to medicines in primary care. However,

our study also suggests that the UCS may have had potentially undesirable effects. Evaluations of the long-term impacts of universal health coverage on medicines utilization are urgently needed.

Introduction

Universal Health Coverage

In 2005, Member States of the World Health Organization (WHO) made a commitment to work towards universal health care coverage.[1] The 2010 WHO World Health Report provides a roadmap for countries to achieve this goal.[2] Universal coverage requires the restructuring of health care and financing systems to improve access to health care services, reduce financial hardship, and increase the efficiency and equity of the health system.[2]

Medicines, which consume 25%–65% of total public and private spending on health in developing countries,[3] present a key challenge to achieving universal coverage. The high spending on medicines, and inefficient use of them, threaten the financial sustainability of a universal coverage scheme. According to the WHO, three of the top ten sources of health care inefficiency involve medicines: high medicine prices and underuse of generics; use of substandard and counterfeit medicines; and inappropriate and ineffective use of medicines.[2] Health insurance systems have several features (e.g., a defined population, access to utilization data, and financial leverage) that give them a unique advantage to reduce out-of-pocket (OOP) expenditures and improve the cost-effective use of medicines through active management strategies involving medicines selection, purchasing, contracting (e.g., physician payment) and utilization management.[4] However, there is little evidence about the impact of health insurance on access to and use of medicines in low- and middle-income countries (LMICs).[4]

The recent implementation of universal health coverage in Thailand presents a unique opportunity to measure the impact of health insurance expansion and hospital payment changes

(the majority of the population is now covered under a closed-ended payment scheme[5]) on utilization of medicines.

Universal Health Coverage in Thailand

With the implementation of the UCS in 2001, Thailand became one of the first LMICs to achieve universal coverage.[6,7] The reform preserved the formal sector workforce schemes: the Social Security Scheme (SSS) for private sector employees (7.2% of the total population in 2001) and the Civil Service Medical Benefit Scheme (CSMBS) for government employees and their dependents (8.5%).[8] The UCS covered those previously enrolled in a voluntary health card (VHC) scheme (20.8%), in private health insurance (2.1%), or in a tax-based, means-tested Low Income Scheme (LIS) for the poor, elderly, children and disabled (32.4%)[8,9] as well as more than one quarter (29.0%) of the population without previous insurance.[8] The UCS was rolled out to all provinces between April and October 2001.[6] By 2004, 95.5% of the population was insured, with three-quarters (75.2%) of the population covered by the UCS.[6]

In addition to coverage expansion, the reform also dramatically altered the mechanism for hospital payment. Before the reform, hospitals were accustomed to fee-for-service (FFS) payments from most insurance schemes, aside from SSS, and the uninsured, who paid OOP per service (i.e., user fees).[10] The majority of user fee spending was on medicines.[11] After the reform, FFS payment only applied to CSMBS patients and for the majority of patients, now UCS enrollees, hospitals were paid on a closed-ended basis[5] for all covered services, including medicines.

The UCS is a compulsory, tax-financed scheme with comprehensive coverage of inpatient and outpatient services, including medicines on the National List of Essential Medicines (NLEM).[6] Individuals must enroll in the scheme at a local Contracting Unit for Primary Care (CUP),[6] primarily housed in government-owned hospitals.[12] Each CUP receives a capitated payment per registered member to provide outpatient services and medicines.[6] CUPs initially served as gate-keepers for secondary and tertiary hospitals. At the beginning of the scheme, when patients were referred, diagnosis-related payments (DRG) for higher-level care had to come out of the CUP's capitated payment, so CUPs had a financial disincentive to refer patients.[6] Shortly after the reform was implemented, a separate fund (i.e., a global budget) for inpatient services was created, which likely reduced disincentives to refer created by the capitated payment scheme.[6] A capitated payment also creates financial incentives for use of lower cost medicines (e.g., generics or less expensive therapeutic alternatives).

Our objective was to evaluate the immediate, short-term (one year) and long-term (five year) impacts of the UCS on pharmaceutical market size and composition for medicines for three non-communicable diseases (NCDs): cancer, cardiovascular disease, and diabetes. We hypothesized that the UCS would result in a gradual increase in sales volume, particularly of products used in primary care, as enrollment into the scheme increased and likely made access to health services and medicines more affordable for the majority of the population. We also hypothesized that there would be an immediate shift in market share from more expensive brand name to less expensive generic or branded generic products and to medicines on the NLEM in response to closed-ended reimbursement rules. We focused on medicines for NCDs since these illnesses

represent a large and growing health care burden in Thailand[13–16] and other LMICs[17] and most, but not all, medicines for NCDs would be prescribed and dispensed in primary care settings.

Methods

Data

We used data on quarterly pharmaceutical sales in Thailand from 1998 to 2006 provided by IMS Health.[18] The sales data are generated from reports to IMS Health by multinational pharmaceutical companies and surveys of purchases by hospital and retail pharmacies. IMS surveys approximately 200 hospitals (including general and specialized, public and private) and 350 retail pharmacies in Thailand. These facilities constitute a stratified random sample of the over 1,100 hospitals and 14,000 retail pharmacies in Thailand to enable national projections. Documentation on the IMS data collection and validation process is available upon request from the authors. Medicines were classified according to the European Pharmaceutical Research Association (EphMRA) Anatomical Therapeutic Chemical (ATC) system.[19]

Outcomes

We used two outcome measures: total volume and percent market share. *Total volume* is the number of standard units purchased per capita per quarter (i.e., "sales"). We analyzed total volume by sector (i.e., retail versus hospital). A standard unit, as defined by IMS Health, is the smallest dose of a product, which equates to one tablet or capsule for an oral dosage form, one teaspoon (5ml) for a syrup, and one ampoule or vial for an injectable product. For the total volume analyses, we divided total volume by size of the population over 15 years old to control for population growth (using yearly population estimates from the World Bank[20]). We used the entire population as denominator for insulins, since they are also used for Type 1 diabetes, a

chronic disease that affects children. *Percent market share* is the percent of total volume in four mutually exclusive categories of licensing status: originator brand products, branded generic products (products sold under a brand name other than the originator brand name of the molecule), generic products (products that are sold under the generic molecule name), and products manufactured by Thailand's Government Pharmaceutical Organization (GPO). We also assessed percent market share by NLEM status (based on the 1999 and 2004 Thai NLEM).

We analyzed total volume and market share for medicines in eight therapeutic classes: two classes of diabetes products (oral antidiabetics and insulins), three classes of cardiovascular disease products (antihypertensives, lipid-regulating, and cardiac therapy products) and three classes of cancer products (antineoplastics, immunostimulating agents, and cytostatic hormone therapy products); Table 1 in Appendix 1 lists all medicines by ATC code. We assigned each therapeutic class to one of two categories: medicines usually used to treat primary care health conditions and medicines usually used to treat more complicated conditions, typically in secondary/tertiary, often inpatient care, settings. Antidiabetic, insulin, antihypertensive and lipid-lowering products are usually used for primary care conditions (i.e., diabetes, high blood pressure and high cholesterol), whereas cardiac therapy and cancer products are usually used for more severe conditions that more likely require treatment by a specialist and/or in an inpatient setting.

Research Design

We used an interrupted time series design, the strongest quasi-experimental approach for evaluating effects of interventions, which has been used extensively for medication use

research.[21] Although we did not have an equivalent control group, we used medicines sold in the retail sector as a non-equivalent comparison group,[22] assuming that the retail market should be relatively unaffected by the reforms since UCS enrollees could only obtain covered medicines through their local, hospital-based CUP.

Statistical Analysis

The intervention was the UCS roll-out from April to October 2001. We defined three distinct periods: 12 quarters pre-reform (1998Q2-2001Q1), a 3-quarter UCS roll-out period (2001Q2-2001Q4; grey box in figures), and 19 quarters post-reform (2002Q1-2006Q3). We ended analysis prior to 2006Q4 since there was a policy change at that time (the removal of an initial 30 Baht co-payment per visit) which may have impacted outcomes. In sensitivity analyses, we extended the intervention roll-out period through 2002 and through 2003 to account for potentially delayed implementation and lag of actual enrollment into the scheme.

We used segmented linear regression to measure the pre-reform trend, the immediate level change following the intervention period, and the post-reform change in trend (as compared to the pre-reform trend). For the NLEM analysis, we reclassified NLEM status in 2005Q1 (when the 2004 list was implemented) and included a pre-post term ("NLEM") in the model to account for possible discontinuity due to the reclassification. We report two estimates from the segmented regression models – the post-reform change in trend and the immediate level change following the reform. We controlled for serial autocorrelation using an autoregressive error model. We retained all terms in the models, even if non-significant. We used the models to estimate absolute and relative differences (with 95% confidence intervals)[23] in observed versus

predicted total volume at one year and five years post-reform. In sensitivity analyses, we included a quadratic term for the post-reform trend and used a likelihood ratio test to determine the best-fitting model. We report below results from the best-fitting model of the shortest (i.e., 3 quarter) intervention period and mention differences in model results where they existed. Results from sensitivity analyses are available upon request. We used the AUTOREG procedure in SAS 9.3 for all analyses.

Results

Hospital Sector Volume

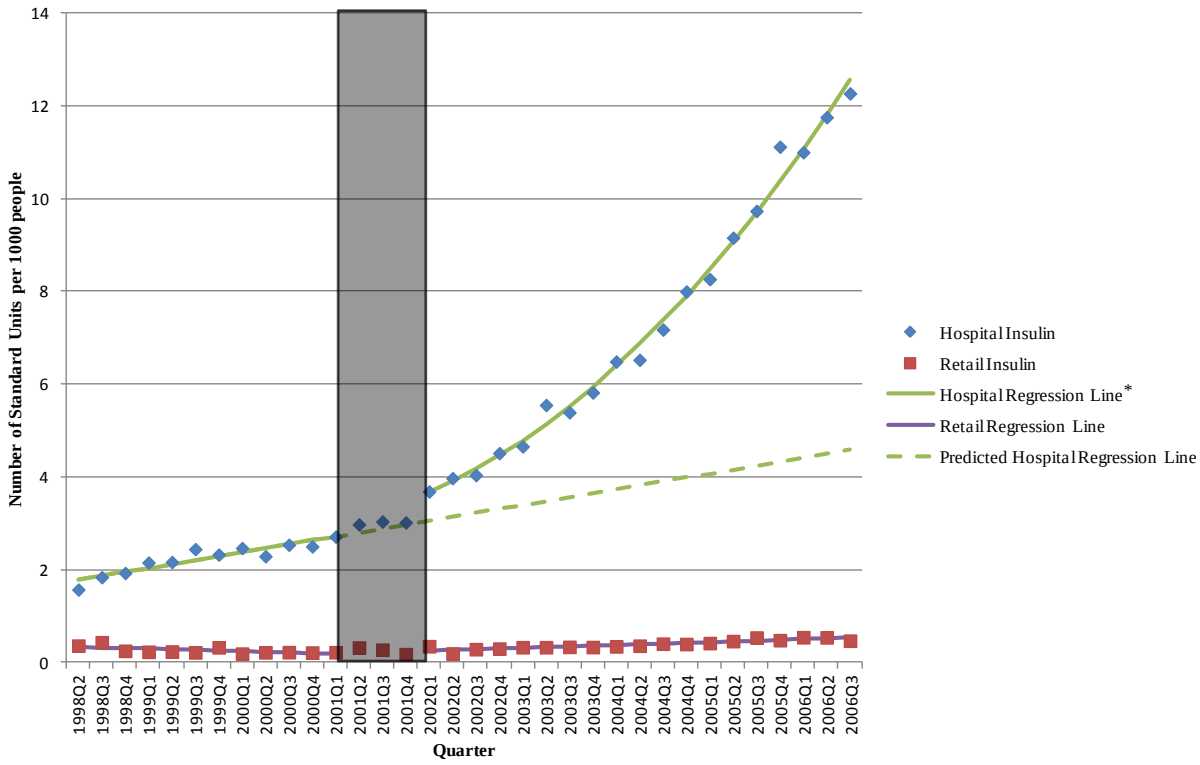
The majority of sales in Thailand for all cancer, cardiovascular disease and diabetes medicines studied were in the hospital sector and were for medicines on the NLEM. After implementation of the UCS, there was a significant increase in *level* of sales of insulins and a significant increase in *trend* in sales of antidiabetic, insulin, antihypertensive, lipid regulating, and cytostatic hormone products [Table 1.1, Figures 1.1 and 1.2]. There was a significant reduction in *level* of sales immediately following the reform for three medication classes: antihypertensive, cardiac therapy and immunostimulating agents (although only the latter was significant in the sensitivity analyses using a longer intervention period) [Table 1.1, Figures 1.1 and 1.2].

Table 1.1 Summary of the Impact of the Universal Coverage Scheme on Volume of Medicine Sales in the Hospital Sector (from segmented regression results) *

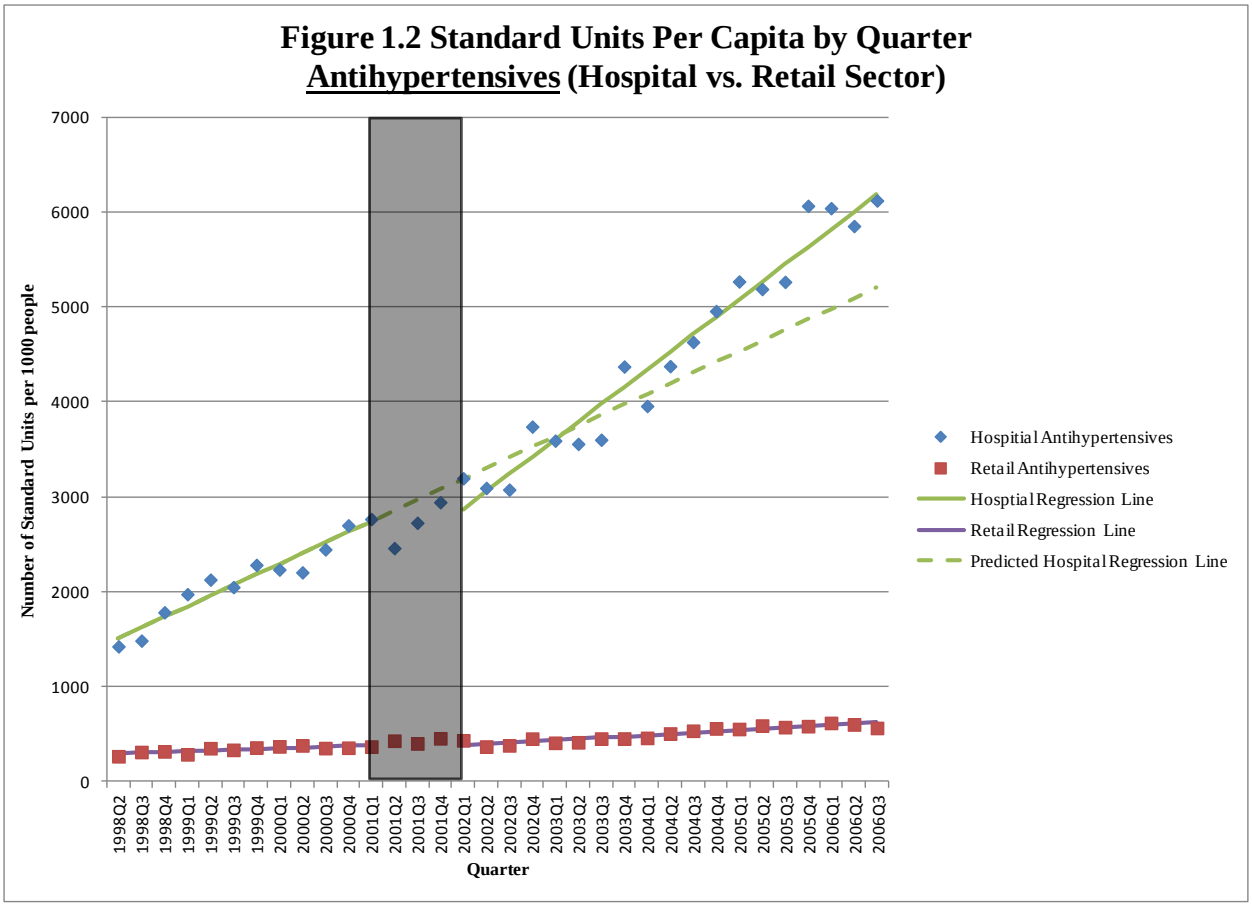
Therapeutic Area	Pre-policy trend	Immediate change after policy	Post-policy trend change
DIABETES			
Antidiabetics**	↑		↑
Insulins**	↑	↑	↑
CARDIOVASCULAR DISEASE			
Antihypertensives	↑	↓	↑
Lipid Regulating Agents**	↑		↑
Cardiac Therapy	↑	↓	
CANCER			
Antineoplastics	↑		
Cytostatic Hormones	↑		↑
Immunostimulating Agents**	↑	↓	

*Arrows signify a statistically significant coefficient ($p<0.05$) from segmented regression with linear post-policy trend term, unless noted otherwise.
**Quadratic model (which has a squared post-policy trend term) fits better than linear model.
Note: See Appendix 1 Table 2 and Figures 1-8 for regression coefficients and figures for all therapeutic areas.

Figure 1.1 Standard Units Per Capita by Quarter
Insulins (Hospital vs. Retail Sector)



*Results from quadratic model



The UCS was associated with increased sales of diabetes medicines. One year after the policy, the sale of insulin was 35% (95% CI: 15%, 55%) higher and, at five years, 174% (95% CI: 114%-235%) higher than what would have been expected in the absence of the UCS [Table 1.2]. The increase in insulin sales was driven primarily by human insulins, which are on the NLEM and marketed as branded generics by two manufacturers. The policy was associated with a 39% (95% CI: 14%, 64%) increase in antidiabetic product sales five years after implementation [Table 1.2]. This was largely due to increased sales of generic and branded generic metformin and glibenclamide products, both of which are on the NLEM.

Table 1.2 Relative Impact of UCS on Sales of Medicines by Class (one and five years post policy)*

Therapeutic Class	One Year Impact (in standard units)			Five Year Impact (in standard units)		
	Predicted	**Observed**	**Relative Change (95% CI)**	**Predicted**	**Observed**	**Relative Change (95% CI)**
Antidiabetics	2602.91	2769.79	6.4% (-6.9, 19.7)	3669.13	5090.62	**38.7% (13.5, 64.0)**
Insulins	3.30	4.45	**34.8% (15.1, 54.5)**	4.58	12.56	**174.4% (113.9, 235.0)**
Cardiac Therapy Agents	699.28	607.27	-13.2% (-26.9, 0.6)	908.12	825.49	-9.1% (-31.9, 13.1)
Lipid Regulating Agents	522.34	504.58	-3.4% (-19.9, 13.1)	781.97	1629.11	**108.3% (59.8, 156.9)**
Antihypertensives	3521.47	3418.79	-2.9% (-15.5, 9.7)	5200.86	6177.49	18.8% (-2.8, 40.3)**
Antineoplastics	35.38	34.21	-3.3% (-15.4, 8.7)	46.14	48.13	4.3% (-16.3, 24.9)
Cytostatic Hormones	29.48	30.58	3.7% (-10.1, 17.6)	39.82	47.52	19.3% (-5.1, 43.8)
Immunostimulating Agents	0.65	0.43	**-35.0% (-45.1, -25.0)**	0.81	0.60	**-26.3% (-45.0, -7.6)**

***Bold** signifies that the change is statistically significant (i.e., confidence interval does not include the null value of 0).
** The *absolute* five-year difference, which is estimated using more precise method, is significant. See Appendix 1 Table 3

Implementation of the UCS appears to have had a mixed impact on sales of cardiovascular medicines. Five years after the policy, the sale of lipid lowering agents was nearly double (108% increase; 95% CI: 60%, 157%) what would have been expected in the absence of the scheme [Table 1.2]. The increase was primarily due to sales of branded generic simvastatin and gemfibrozil products, which are on the NLEM, and a small but steady increase in sales of originator atorvastatin products, which were not on the NLEM until 2004. For antihypertensives, the significant increase in post-policy trend compensated for an initial drop in sales, resulting in a slight increase in sales five years after the policy (19% increase; 95% CI: -3%, 40%) [Figure 1.2, Table 1.2]. The increased trend was primarily due to sales of enalapril, atenolol, and amlodipine, all of which are on the NLEM and predominately sold as branded generics. The reform had no significant impact on sales of cardiac therapy medicines one or five years after the policy.

The results were also mixed for cancer medicines. The UCS had no significant one- or five-year impact on the sale of antineoplastics or cytostatic hormones (although the latter class did experience a significant post-policy increase in trend). However, the policy was associated with an immediate reduction in sales of immunostimulating agents that did not recover in the post-policy period. One year after implementation, the sale of immunostimulating agents was 35% lower (95% CI: -45%, -25%) than expected from pre-policy trends, and 26% lower (95% CI: -45%, -8%) five years post-policy. This drop is almost entirely due to a sharp reduction in sales of interferon alfa-2b, a non-NLEM medicine, around the time of UCS implementation, which could have been due to a coincidental recall of an interferon alfa-2b product.[24]

Finally, as expected, the reform had little impact on sales volume in the retail sector – there were few significant post-implementation changes, and the changes that were significant were small in magnitude [see Appendix 1 Table 2].

Hospital Sector Market Share

Immediately following the reform, there were significant shifts in hospital sector market share by licensing status for most classes [Table 1.3]. The changes for antidiabetics and cardiac medicines - the two therapeutic classes with the largest shifts – were due to significant increases in GPO-produced medicines, primarily at the expense of branded generics and, to a lesser extent, generics. There was a significant increase in GPO antidiabetic products (+16% of market; 95% CI: 12%, 20%), and decreases in branded generic (-12%; 95% CI: -16%, -9%) and generic (-4%; 95% CI: -6%,-1%) products immediately after the policy [Figure 1.3]. Similarly, there was a significant increase in GPO cardiac therapy products (+22%; 95% CI: 15%, 28%), and

significant decreases of branded generic (-14%; 95% CI:-21%, -7%) and generic (-4%; 95% CI:-6%, -2%) products immediately after the policy [Figure 1.4]. There was also a small decrease in market share of generic antihypertensives (-6%; 95% CI: -8%, -3%), which was compensated by a marginally significant increase in GPO products.

Table 1.3 Immediate Impact of UCS on Hospital Sector Market Share*

Therapeutic Area	Licensing Status	Immediate post-policy absolute change in % market share (95% CI)
DIABETES		
Antidiabetics	Originator brand	-0.3% (-1.6, 1.0)
	Branded generic	**-12.3% (-16.0, -8.7)**
	Generic	**-3.5% (-5.8, -1.1)**
	GPO	**16.1% (12.0, 20.2)**
Insulins***	Originator brand**	-0.04% (-0.4, 0.3)
	Branded generic	**7.0% (2.9, 11.1)**
	Generic	**-6.2% (-10.3, -2.1)**
CARDIOVASCULAR DISEASE		
Antihypertensives	Originator brand**	-0.1% (-2.3, 2.0)
	Branded generic**	-0.2% (-6.1, 1.8)
	Generic	**-5.7% (-8.3, -3.0)**
	GPO	5.3% (-0.1, 10.6)
Lipid Regulating Agents	Originator brand**	**-7.8% (-10.2, -5.4)**
	Branded generic**	**7.6% (5.1, 10.0)**
	Generic	0.2% (-0.4, 0.7)
	GPO	0.2% (-0.3, 0.8)
Cardiac Therapy	Originator brand	0.1% (-0.8, 1.0)
	Branded generic**	**-13.5% (-20.5, -6.5)**
	Generic	**-4.3% (-6.2, -2.4)**
	GPO	**21.6% (15.0, 28.1)**
CANCER***		
Antineoplastics	Originator brand	1.1% (-1.0, 3.2)
	Branded generic	-1.0% (-5.4, 3.4)
	Generic	0.4% (-2.7, 3.4)
Cytostatic Hormones	Originator brand**	0.4% (-5.4, 6.1)
	Branded generic**	**-7.7% (-12.0, -3.5)**
	Generic**	**6.0% (1.4, 10.6)**
Immunostimulating Agents	Originator brand	**-6.4% (-9.7, -3.0)**
	Branded generic	**4.5% (1.7, 7.3)**
	Generic	-0.2% (-0.3, 0.02)

*__Bold__ signifies a statistically significant regression coefficient ($p<0.05$). Changes are in absolute terms (i.e., percentage point change).
**Quadratic model (which has a squared post-policy trend term) fits better than linear model.
***GPO did not produce any insulins or cancer medicines during the study period.
Note 1: See Appendix 1 Table 4 and Figures 9-16 for market share regression coefficients and figures for all therapeutic areas
Note 2: Aside from the immediate level changes following the policy, there were few major changes in market share. See Appendix 1 Table 5 for absolute one- and five-year differences.

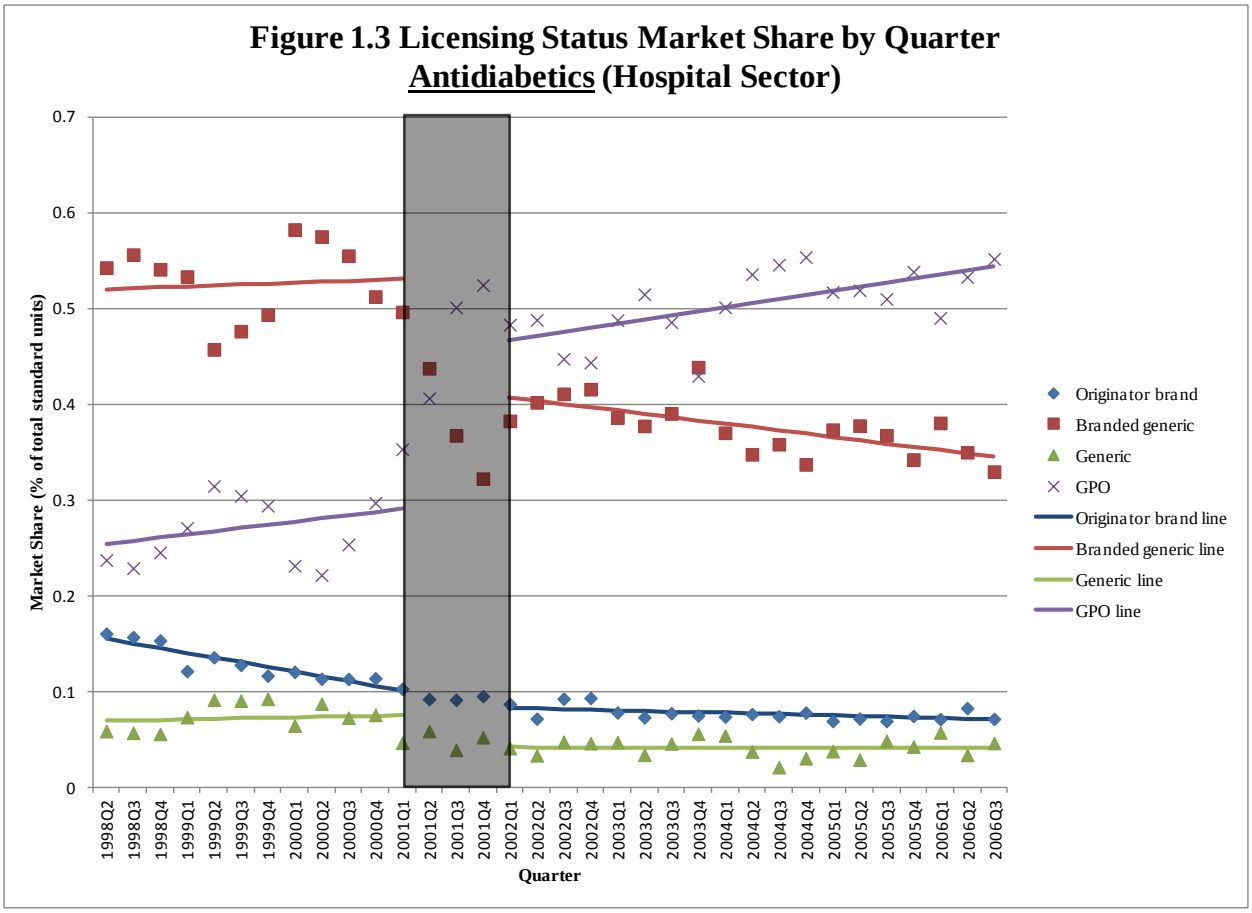
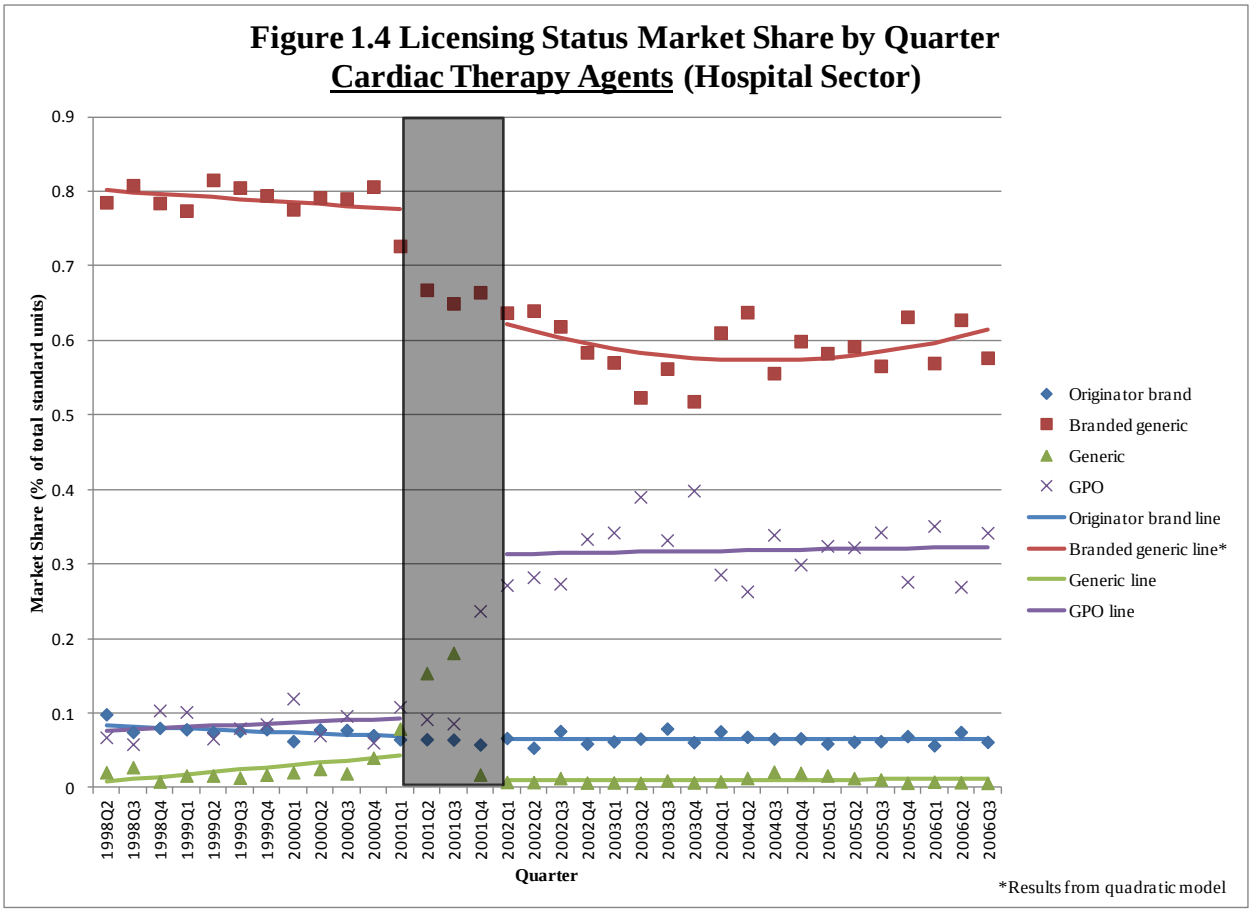


Figure 1.3 Licensing Status Market Share by Quarter
Antidiabetics (Hospital Sector)
Market Share (% of total standard units)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1998Q2
1998Q3
1998Q4
1999Q1
1999Q2
1999Q3
1999Q4
2000Q1
2000Q2
2000Q3
2000Q4
2001Q1
2001Q2
2001Q3
2001Q4
2002Q1
2002Q2
2002Q3
2002Q4
2003Q1
2003Q2
2003Q3
2003Q4
2004Q1
2004Q2
2004Q3
2004Q4
2005Q1
2005Q2
2005Q3
2005Q4
2006Q1
2006Q2
2006Q3
Quarter
Originator brand
Branded generic
Generic
GPO
Originator brand line
Branded generic line
Generic line
GPO line



The market for lipid regulating agents experienced an immediate shift from originator products (-8% market share; 95% CI:-10%, -5%) to branded generics (+8%; 95% CI:5%, 10%). A similar shift was seen for in the market for immunostimulating agents (6% decrease in originator products [95% CI:-10%, -3%] and a 5% increase in branded generics [95% CI:2%, 7%]). The cytostatic hormone market experienced an immediate shift from branded generic (-8%; 95% CI:-12%, -4%) to generic products (+6%, 95% CI: 1%, 11%). Generic insulins experienced a slight decrease in market share caused by the market exit of the sole generic manufacturer just prior to the policy. There were no immediate changes in market share for antineoplastics. Aside from the

immediate level changes following the policy, there were few major changes in market share for all classes.

The UCS did not have a major impact on NLEM market share, likely because the share of NLEM medicines was already quite high [see Appendix 1 Table 6 and Figure 17]. The only notable level change, for immunostimulating agents, was likely due to the coincidental recall of a non-NLEM interferon alfa-2b product.[24] While all medicine classes had significant post-reform trends, these trends were small in magnitude and NLEM market share remained fairly stable over the study period until the 2004 NLEM was introduced. There were large changes in NLEM market share for three classes – antihypertensives, lipid regulating agents and cytostatic hormones – at the time of the 2004 NLEM implementation in 2005Q1 [see Appendix 1 Table 6 and Figure 17]. Given the increase in post-reform volume for many medicine classes, a stable NLEM market share in the short-term (i.e., pre-2005) following the UCS implementation suggests a post-reform increase in both NLEM and non-NLEM medicines.

Discussion

The UCS was associated with long-term (i.e., 5 year) increases in hospital sector sales of medicines for chronic diseases that are usually treated in primary care settings, such as diabetes, high blood pressure, and high cholesterol. We hypothesized this gradual increase in volumes since the UCS expanded access to primary care[25] and actual enrollment into the scheme occurred gradually from implementation in 2001 until around 2004, by which time 95.5% of the population had insurance coverage.[6] The UCS, which radically changed hospital financing and

reimbursement, was also associated with an immediate market shift to locally produced or branded generic products for most therapeutic classes.

Despite these increases in access, the policy did not appear to increase sales of medicines for more severe diseases like heart failure, arrhythmias, and cancer, which are often treated in secondary or tertiary settings. This finding is consistent with evidence that the capitated payment system initially discouraged referrals of UCS patients to higher-level care.[6,25,26] The UCS also appears to have had a mixed impact on utilization of essential medicines. There were increases in NLEM medicines, which are covered, as well as non-NLEM medicines. Similarly, given the capitated UCS payment system, we expected to see an increase in sales of generic medicines, which are typically less expensive. However, the majority of sales in most classes were for branded generic products, many of which had generic alternatives in the market. Interestingly, substantial market share shifts occurred toward products manufactured by the Thai GPO, which have been noted to have higher than market prices.[27] By law, GPO products received preferential status by hospital purchasers,[28] which negates the incentive to prescribe cheaper alternatives under the capitated payment system. While the increase in GPO products and the UCS implementation may be a coincidence in timing, it is noteworthy that the GPO expanded its product line at a time when the UCS policy expanded the market of people who could afford medicines.

Our study demonstrates the value of IMS Health market intelligence data for rigorous health policy evaluation. Unlike other sources of data on pharmaceutical utilization (i.e., national health surveys or ad hoc hospital surveys), IMS data represent country pharmaceutical markets

consistently over time and are useful for the evaluation of system-wide interventions. Nevertheless, the data pose some limitations. Aggregate national sales data do not allow us to determine whether observed increases in medicines sales occurred preferentially among UCS enrollees or enrollees in the SSS and CSMBS schemes, conceivably to compensate for financial strain of the UCS on hospital budgets.[6] CSMBS expenditures increased following UCS implementation[29] and increased medicines sales among CSMBS enrollees, reimbursed on a fee-for-service basis, could explain increases in non-NLEM medicines and medicines with less expensive therapeutic alternatives.[5] However, it is unlikely that increased utilization among CSMBS enrollees explains most of the observed volume changes since this would imply that one-half (for diabetes) to three-quarters (for hypertension) of CSMBS members (7.1% of the total population in 2004[6]) were on these treatments in 2004. Even the CSMBS and SSS schemes combined (20.3% of the total population in 2004[6]) are unlikely to be responsible for the observed changes since this would imply that one-quarter (for diabetes) and one-third (for hypertension) of enrollees in the two schemes were on these treatments in 2004. These estimates are much higher than the national prevalence (6.7% for diabetes[30] and 22.0% for hypertension[31] in 2004) and unlikely in the civil servant and private sector workforce populations, which are likely to be healthier and wealthier than the national average.

Our interpretation of the observed changes assumes that pharmaceutical sales to hospital and retail pharmacies reflected total market utilization, and that hospital sales volumes included utilization at affiliated primary care units. This assumption seems justified in light of the estimated 91% accuracy of IMS Health data in representing the Thai pharmaceutical market.[32] For local generic products, including those produced by the GPO, IMS Health data are based on

pharmacy surveys only (as opposed to pharmacy surveys and manufacturer reports), so we may have underestimated utilization. However, unless this systematic underestimation changed at the point of the UCS implementation, it would not have impacted our results. Finally, since we did not convert standard units of product sold to defined daily doses (DDD), we do not describe sales changes in terms of average adult doses.

There are also potential limitations due to study design and statistical analysis. We addressed the main threat to the internal validity of the interrupted time series design – a concurrent event that affects the outcome of interest – by assessing other policies or market events that occurred at the time of the UCS, through literature reviews, discussions with in-country experts, and by including the retail sector as a comparison. The statistical approach, segmented regression analysis, usually assumes a linear trend and well-defined break point. Sensitivity analyses that varied model specification and intervention duration did not change the findings. By reporting results from fully-specified models, we may have underestimated the statistical significance of one- and five-year change estimates.

While both the context and the implementation of universal coverage in Thailand are unique and not necessarily generalizable to other LMICs, our findings suggest that expanding health insurance coverage with a medicines benefit to the entire population, together with changes in the payment system and increased local manufacturing, increased the per capita volume of medicines sold and, by inference, improved access to medicines in the primary care sector in Thailand, presumably by making medicines more affordable. Since the study period, Thailand has enacted further policies to address pharmaceutical sector cost escalation (e.g., strict

enforcement of reimbursement for only NLEM medicines in the CSMBS[33]) and to ensure appropriate access to non-NLEM medicines (e.g., coverage of medicines for HIV, renal replacement therapy, and mental health conditions).[34–36] In the future, it will be important for Thailand and other countries to assess equity in access to and quality of use of medicines, availability of medicines in health centers and hospitals, out-of-pocket and system expenditures and affordability, and health outcomes as they pursue policies to achieve universal coverage.

REFERENCES

1 World Health Organization. Resolution from the fifty-eight World Health Assembly. Sustainable health financing, universal coverage and social health insurance (WHA58.33) [Internet]. 2005 [cited 2011 Mar 8]. Available from: http://www.who.int/providingforhealth/topics/WHA58_33-en.pdf.

2 World Health Organization. 2010 World Health Report: Health systems financing: the path to universal coverage [Internet]. 2010 [cited 2011 Mar 8]. Available from: http://www.who.int/whr/2010/en/index.html.

3 J. Quick. Ensuring access to essential medicines in developing countries—A framework for action. *Clinical Pharmacology and Therapeutics.* 2003;**73**(4): 279–283.

4 Faden L, Vialle-Valentin C, Ross-Degnan D, Wagner A. Active pharmaceutical management strategies of health insurance systems to improve cost-effective use of medicines in low- and middle-income countries: a systematic review of current evidence. *Health Policy*. 2011;100(2-3):134-143.

5 Hirunrassamee S, Ratanawijitrasin S. Does your health care depend on how your insurer pays providers? Variation in utilization and outcomes in Thailand. *Int J Health Care Finance Econ*. 2009;9(2):153-168.

6 Hughes D, Leethongdee S. Universal coverage in the land of smiles: lessons from Thailand's 30 Baht health reforms. *Health Aff (Millwood).* 2007;26(4):999-1008.

7 The Rockefeller Foundation. Catalyzing Change: The System Reform Costs of Universal Health Coverage [Internet]. 2010 Nov 15 [cited on 2011 Mar 8]. Available from: http://www.rockefellerfoundation.org/news/publications/catalyzing-change-system-reform-costs.

8 Tangcharoensathien V, Prakongsai P, Limwattanon S, Patcharanarumoi W, Jongudomsuk P. Achieving universal coverage in Thailand: what lessons do we learn? [Internet]. 2007 March [cited on 2012 September 25]. Available from: http://www.who.int/social_determinants/resources/csdh_media/universal_coverage_thailand_2007_en.pdf

9 Tangcharoensathien V, Wibulpholprasert S, Nitayaramphong S. Knowledge-based changes to health systems: the Thai experience in policy development. *Bull. World Health Organ*. 2004;82(10):750-756.

10 Pitaknetinan K, Tangcharoensathien V, Supachutikul A, Bennett S, Mills A. Profit, payment and pharmaceutical practices: Perspectives from hospitals in Bangkok. *Health Policy.* 1999;46(3):179–194.

11 World Bank. Waivers and exemptions for health services in developing countries [Internet]. 2002 October [cited on 2012 October 1]. Available from:

http://siteresources.worldbank.org/SOCIALPROTECTION/Resources/SP-Discussion-papers/Safety-Nets-DP/0308.pdf

12 NaRanong V, NaRanong, A,Treamworakul S. Universal Health Coverage Schemes in Thailand 2002-2003. Research Report No.1: Monitoring and Evaluating Universal Health Care Coverage in Thailand, Phase II, 2003-04. Bangkok: Thailand Development Research Institute; 2004.

13 Kaufman N, Chasombat S, Tanomsingh S, Rajataramya B, Potempa K. Public health in Thailand: emerging focus on non-communicable diseases. *Int J Health Plann Manage.* 2011; 26(3): e197-212

14 Bundhamcharoen K, Odton P, Phulkerd S, Tangcharoensathien V. Burden of disease in Thailand: changes in health gap between 1999 and 2004. *BMC Public Health*. 2011;11:53.

15 World Health Organization. Thailand: Health Profile [Internet]. 2011 Apr 11[cited 2012 Feb 8]. Available from: http://www.who.int/gho/countries/tha.pdf

16 Porapakkham Y, Rao C, Pattaraarchachai J, et al. Estimated causes of death in Thailand, 2005: implications for health policy. *Population Health Metrics*. 2010;8(1):14.

17 Beaglehole R, Bonita R, Horton R, et al. Priority actions for the non-communicable disease crisis. *Lancet*. 2011;377(9775):1438-1447.

18 IMS Health MIDAS. 1998-2006.

19 European Pharmaceutical Market Research Association (EphMRA). Anatomical Classification [Internet]. 2012 [cited 2012 Feb 6]. Available from: http://www.ephmra.org/classification/anatomical-classification.aspx

20 The World Bank. Data [Internet]. 2011 [cited 2011 May13]. Availalble from: http://data.worldbank.org/

21 Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther*. 2002;27(4):299-309.

22 Shadish WR, Cook TD, Campbell DT. Experimental and quasi-experimental designs for generalized causal inference. Boston: Houghton Mifflin Company; 2002.

23 Zhang F, Wagner AK, Soumerai SB, Ross-Degnan D. Methods for estimating confidence intervals in interrupted time series analyses of health interventions. *J ClinEpidemiol*. 2009;62(2):143-148.

24 United States. Food and Drug Agency.Recall of Interferon alfa-2b, (Recombinant), Powder for Injection, Intron A - (Schering Corporation) [Internet]. 2001 Oct 22 [cited 13 Oct 2011]. Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113617.htm

25 Damrongplasit K, Melnick GA. Early results from Thailand's 30 Baht Health Reform: something to smile about. *Health Aff (Millwood).* 2009;28(3):w457-466.

26 Yiengprugsawan V, Carmichael G, Lim L, Seubsman S, Sleigh A. Explanation of inequality in utilization of ambulatory care before and after universal health insurance in Thailand. *Health Policy Plan*. 2011; 26(2): 105-14.

27 Ten Kate D. Safe at any costs? Asia Sentinel (Hong Kong) [Internet]. 2001 Jan 4 [cited 2012 Feb 6]. Available from: http://www.asiasentinel.com/index.php?option=com_content&task=view&id=351&Itemid=392

28 Ratanawijitrasin S. Pharmaceutical policy in Thailand: a review of three decades of government interventions. In: Eggleston K, editor. Prescribing cultures and pharmaceutical policy in the Asia Pacific. Stanford: The Walter H. Shorenstein Asia-Pacific Research Center Books; 2009. p. 79–106.

29 Tangcharoensathien V, Jongudomsuk P. From policy to implementation: Historical events during 2001-2011 of universal coverage in Thailand. Bangkok, Thailand: National Health Security Office; 2012.

30 Aekplakorn W, Abbott-Klafter J, Premgamone A, et al. Prevalence and management of diabetes and associated risk factors by regions of Thailand: Third National Health Examination Survey 2004. *Diabetes Care.* 2007;30:2007–2012

31 Aekplakorn W, Abbott-Klafter J, Khonputsa P, Tatsanavivat P, Chongsuvivatwong V, Chariyalertsak S, et al. Prevalence and management of prehypertension and hypertension by geographic regions of Thailand: the Third National Health Examination Survey, 2004. *J Hypertens.* 2008; 26:191–198.

32 IMS Health. IMS Thailand Market Prognosis. 2012.

33 IMS Health. Pharma Pricing and Reimbursement. 2011 Mar; 16(3).

34 Khanna R. Universal Health Coverage in Thailand: What Lessons Can India Learn? [Internet]. 2010 Dec 16 [cited 2012 Feb 7]. Available from: http://www.mfcindia.org/main/bgpapers/bgpapers2011/am/bgpap2011r.pdf

35 Treerutkuarkul A. Thailand: health care for all, at a price. *BullWorld Health Organ*. 2010; 88(2): 84-5.

36 Pitayarangsarit S. The Introduction of the Universal Coverage of Health Care Policy in Thailand: Policy Responses [PhD thesis]. London, UK: London School of Hygiene and Tropical Medicine; 2004 [cited 2012 Feb 7]. Available from: http://www.nhso.go.th/eng/download/The%20Introduction%20of%20the%20Universal%20Coverage%20of%20Health%20Care%20Policy%20in%20Thailand_%20Policy%20Responses.pdf

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Chapter 2: Massachusetts Health Care Reform: Impact of the Individual Mandate and Health Insurance Exchange on Short-Term Enrollment and Adverse Selection [c,d]

[c] This chapter was co-authored by Jeffrey Brown, Dennis Ross-Degnan, Stephen Soumerai and Niteesh Choudhry.

[d] This project received ethics approval from the Harvard Pilgrim Health Care Institute Office of Sponsored Programs.

ABSTRACT

Background: The 2006 Massachusetts (MA) health insurance reform, which contains provisions – an individual mandate and health insurance exchange - similar to the Patient Protection and Affordable Care Act (PPACA), provides important lessons for the national reform. While MA has achieved near-universal coverage, health insurance market failures may threaten the sustainability of the reform. Widely cited unpublished data suggests that the MA reform increased short-term enrollment and adverse selection in the individual health insurance market.

Objective: To evaluate the impact of the MA reform on short-term enrollment and utilization in the unsubsidized individual health insurance market.

Design: Pre-post survival analysis and interrupted time series design.

Intervention: Implementation of MA health insurance reform on July 1, 2007.

Data: Harvard Pilgrim Health Care (HPHC) administrative and health care utilization claims data from 2004-2010.

Participants: Members ages 18 to 64 in unsubsidized HPHC individual market plans with an enrollment start date between January 2004 and December 2010.

Outcome measures: Probability of disenrollment at 45, 90, 180 and 365 days following enrollment, time from enrollment to disenrollment, and time from enrollment to first medical encounter (ambulatory, emergency department, inpatient and same day surgery) or elective event (knee surgery and infertility treatment).

Results: There were 8,064 individual market HPHC members in the pre-reform cohort and 37,798 in the post-reform cohort. The demographic characteristics of the MA individual market changed significantly after health reform. The unadjusted probabilities of disenrollment within 45, 90, 180 or 365 days of enrollment dropped immediately after the reform and the rate of disenrollment was significantly lower in the post-reform period (hazard ratio (HR)=0.811, 95%

CI: 0.784, 0.838). And, the rates of inpatient (HR=0.830, 95% CI: 0.744, 0.927) and emergency department (HR=0.851, 95% CI: 0.795, 0.911) encounters were significantly lower in the post-reform period. However, rates of infertility treatment were significantly higher after the reform (HR=1.697, 95% CI: 1.325, 2.174).

Conclusions: Contrary to previous reports, we did not find evidence that the MA health reform led to an increase in short-term enrollment in the unsubsidized individual insurance market. We also found little evidence that post-reform members were more likely to have a high cost medical encounter.

Introduction

The 2006 Massachusetts (MA) health care reform mandates that almost all state residents have health insurance coverage or face a financial penalty.[1] To facilitate access to insurance and foster competition, the law merged the small group and individual markets and established the Connector,[2,3] a health insurance exchange for individuals, families and small groups to purchase private health plans that meet state-defined minimum creditable coverage criteria.[1] These key elements of the MA reform – an individual mandate and health insurance exchange - will be implemented as part of the Patient Protection and Affordable Care Act (PPACA)[4,5] on January 1, 2014.[6] Therefore, knowledge of the intended and unintended consequences of the MA health reform provides important lessons for national reform.

The purpose of the individual mandate was to attain near universal coverage and reduce adverse selection (i.e., people enrolling only when they are sick) in the individual market by encouraging young and healthy people to enroll.[7-9] Near universal coverage has been achieved – as of 2010, 98% percent of MA residents were insured.[10] However, a preliminary unpublished report commissioned by the Massachusetts Division of Insurance, Health Care Access Bureau[11] suggested that the reform increased short-term enrollment and adverse selection in the individual market. The report and anecdotal reports[12,13] suggested that some enrollees purchase insurance in anticipation of an expensive medical encounter and then drop coverage after they receive care. These short-term, high-cost enrollees are purported to be young and generally healthy individuals who need expensive, non-urgent procedures such as orthopedic surgery or infertility treatments.

Short-term health plan enrollment itself is not necessarily a problem. In fact, some increases in short-term enrollment are to be expected given that the Connector was designed to capture people in transition (e.g., people between jobs). However, this behavior is problematic for insurers' sustainability if short-term enrollees systematically incur higher than expected costs and it is a red flag for adverse selection if these high-cost services are predictable to the enrollee before enrollment. Adverse selection, a form of market failure that stems from informational asymmetry at the point of enrollment between members and the insurers,[7,14] is not limited to short-term enrollees – this behavior is a concern for insurers regardless of a member's enrollment length.

Both short-term enrollment and adverse selection threaten the sustainability of health care reform through higher than expected costs and subsequent premium increases. An evaluation of the extent of the problem in the MA individual market is both critical and timely, with implications for the sustainability of national health insurance reform. To date, there has been no comprehensive evaluation of the impact of the MA reform on short-term enrollment and adverse selection in the individual insurance market. The Massachusetts Division of Insurance consulting report[11] used crude measurements, did not have patient-level data on demographic characteristics or health utilization, was not peer reviewed, and drew conclusions that were not supported by the reported data.

We set out to evaluate potential unintended consequences of the MA health reform using patient-level data and robust longitudinal methods. We evaluated the impact of the MA reform on enrollment length in the unsubsidized individual market plans offered by the second largest MA

insurer. And, to identify potential adverse selection, we evaluated the impact of the reform on rates of medical care utilization. We examined differences in demographic characteristics and plan characteristics with the goal of explaining consumer behavior. We conclude with policy recommendations and plans for future research.

Methods

Design

Using a pre-post and interrupted time series design, we compared demographic and plan characteristics, disenrollment rates, and hazard ratios for disenrollment and health care utilization among members enrolled in Harvard Pilgrim Health Care (HPHC) individual market health insurance plans in the 3.5 years before ("pre-reform") and 3.5 years after ("post-reform") implementation of the MA health reform on July 1, 2007.

Data Sources

We used HPHC administrative and health care utilization claims data from 2004-2010. HPHC is the second largest insurer in MA, with 20% of the state's total commercial market share.[15] The data included enrollment start and stop dates, insurance plan characteristics, demographic characteristics, and information on medical diagnoses, encounters, procedures and outpatient prescription medicines dispensed. Information on race, family income and education was geocoded at the block level from the 2000 Census.

Study Cohort

We included members in unsubsidized individual market plans with an enrollment start date between January 2004 and December 2010. Member identifiers remain consistent in all HPHC plans; only the first eligible continuous enrollment period was included in the main analysis. We excluded members who were enrolled in Medicare or Medicaid, were 65 years old or older at enrollment end date, or died on or before their enrollment end date. We excluded children (i.e., members age 0-17) from the analyses since children are not responsible for their own enrollment decisions.

We assessed demographic and plan characteristics at the enrollment start date. We assigned members who enrolled before July 1, 2007, when the individual and small group markets merged and the Connector plans became available, to the pre-reform cohort and members who enrolled on or after July 1, 2007 to the post-reform cohort.

Enrollment Length

Membership periods with gaps of 62 days or less were bridged to create a continuous enrollment period; this is consistent with Connector enrollment rules.[16] In sensitivity analyses, we shortened the allowed enrollment gap to 45 days.

Health Care Utilization

We examined four broad categories of utilization: ambulatory visits, emergency department encounters, inpatient stays and same-day surgeries. We also examined two elective procedures that were singled out in the initial media coverage of high cost, short-term enrollment in MA:

infertility treatment and arthroscopic knee surgery.[12] Utilization categories and elective procedures were identified by procedure codes (i.e., DRG, ICD-9, CPT and HCPCS).

Statistical Analysis

We compared baseline demographic characteristics (age, sex, race, family income, education) and insurance plan characteristics (primary vs. dependent status, individual vs. family plan, Health Maintenance Organization [HMO], Preferred Provider Organization [PPO], High Deductible Health Plan [HDHP], prescription drug coverage and mental health coverage) in the pre- vs. post-reform groups. We used t-tests and chi-square tests to test for statistically significant differences.

We compared the probability of disenrollment at 45, 90, 180 and 365 days pre vs. post reform. We removed from the denominator members who enrolled within 45, 90, 180 and 365 days, respectively, of the reform date (for the pre-reform cohort) or study end date (for the post-reform cohort). We used chi-square tests to test for statistically significant differences.

We examined the probability of disenrollment at 45, 90, 180 and 365 days by month of enrollment using segmented linear regression to measure the pre-reform trend, the immediate level change following the reform, and the post-reform change in trend (as compared to the pre-reform trend).[17] Again, we excluded members who enrolled within 45, 90, 180 and 365 days, respectively, of the reform date (for the pre-reform cohort) or study end date (for the post-reform cohort). We report estimates of the immediate level change following the reform. We controlled for serial autocorrelation using an autoregressive error model. We retained all terms in the

models, even if non-significant. In sensitivity analyses, we examined the probability of disenrollment by quarter of enrollment.

We assessed time from enrollment start to disenrollment and time from enrollment start to first encounter for each of the four utilization categories, knee surgery and infertility treatment using survival analysis methods - Kaplan Meier curves and Cox Proportional Hazard models, the latter of which controlled for demographic and insurance plan characteristics. We censored pre-reform members at the reform date (July 1, 2007) and post-reform members at the study end date (December 31, 2010). We stratified the analysis by covariates that had significant interaction terms with the pre-post reform variable. We examined two follow-up periods: the entire study period (up to 3.5 years after enrollment) and one year after enrollment. For all survival models, we used the Wald chi-square statistic to test whether the hazard ratios changed significantly. We assumed the hazard ratios were constant over time, given demographic and plan characteristics. We use the term "rate" when referring to hazard ratios in the results and discussion sections. We used SAS 9.2 for all analyses.

Results

Demographic and Plan Characteristics

There were 8,064 HPHC members in the pre-reform individual market cohort and 37,798 in the post-reform cohort. The demographic characteristics of the MA individual market changed significantly after the health reform [Table 2.1]. Post-reform members were more likely to be male, younger, and to live in areas with a greater proportion of white, non-Hispanic residents and in areas with lower educational attainment and family income. Missing data were negligible -

less than 0.01% of members in the pre and post periods were missing demographic data. In addition, post reform members were more likely to be dependents (i.e., spouse or child), in a family plan, in a PPO or HDHP, and have prescription drug coverage (as mandated by the reform). Most (60%) individual market members enrolled through the Connector. Demographic and plan characteristics for the adult-only population are in Appendix 2 Table 1.

Table 2.1: Demographic and Plan Characteristics, Pre vs. Post Reform

	Massachusetts - Individual Market (n=45,862)	
	Pre-Reform	***Post-Reform***
Number of Members	8,064	37,798
Gender (% male)	42.3	47.1**
Age (mean, std)	33.1 (17.0)	31.2 (17.7)**
Age (distribution):		
Birth-17 years old	14.3	22.7**
18-26 years old ("young adults")	25.5	24.4*
27-40 years old	27.8	21.0**
41-50 years old	12.8	13.3
51-64 years old	19.6	18.6*
Race (mean % white, non-hispanic, std) [a]	87.8 (15.4)	89.3 (14.6)**
Education Level (mean % with ≥ some college, std) [a]	53.4 (19.6)	51.2 (18.9)**
Education Level Categories (mean %) [a]		
Less than 9th grade	3.3 (4.4)	3.4 (4.6)
9th - 12th grade	6.1 (5.1)	6.4 (5.1)*
High school graduate	21.4 (10.9)	22.7 (10.5)**
Some college, no degree	15.6 (5.9)	16.4 (5.9)**
Associate degree	6.6 (3.3)	7.1 (3.5)**
Bachelor degree	25.5 (9.3)	24.9 (9.5)**
Graduate or professional degree	21.4 (14.3)	19.2 (13.3)**
Family Income [a]		
Mean % Family Income <$50,000 (std)	29.8 (16.6)	30.5 (16.7)*
Mean % Family Income $50,000-$99,000 (std)	37.2 (12.1)	38.4 (12.2)**
Mean % Family Income >$100,000 (std)	33.0 (20.0)	31.1 (19.5)**
Primary Member (% who were subscriber)	78.2	60.3**
Dependent Member		
Spouse (% who are married to subscriber)	7.3	13.0**
Child (% who are a child of subscriber)	14.6	26.7**
Contract Type		
Individual (% of members in individual plan)	69.3	44.3**
Family (% of members in plan with at least one other person)	30.7	55.8**
Connector (% in Connector plan, post-reform only)	NA	59.80
Plan Characteristics		
HMO (% in HMO plan)	100	87.9**
PPO (% in PPO plan)	0.09	12.2**
HDHP (% in HDHP)	0	7.2**
Prescription Drug Coverage (% with Rx benefit)	44.2	85.3**
Mental Health Coverage (% with MH coverage)	100	100

[a] % in census block of residence (education is % of population age 25+ in that level)

* post significantly different than pre, $p<0.05$

** post significantly different than pre, $p<0.0001$

Enrollment Length

The probabilities of disenrollment within 45, 90, 180 or 365 days of enrollment were significantly lower for post-reform members [Figure 2.1]. In the segmented regression analysis, the probabilities of disenrollment within 45, 90, 180 or 365 days dropped significantly immediately following the reform in the unadjusted models [Table 2.2, Figure 2.2, Appendix 2 Table 2]. For example, the probability of disenrollment within 180 days dropped by 10.35 (std. err. 2.96) percentage points immediately following the reform.

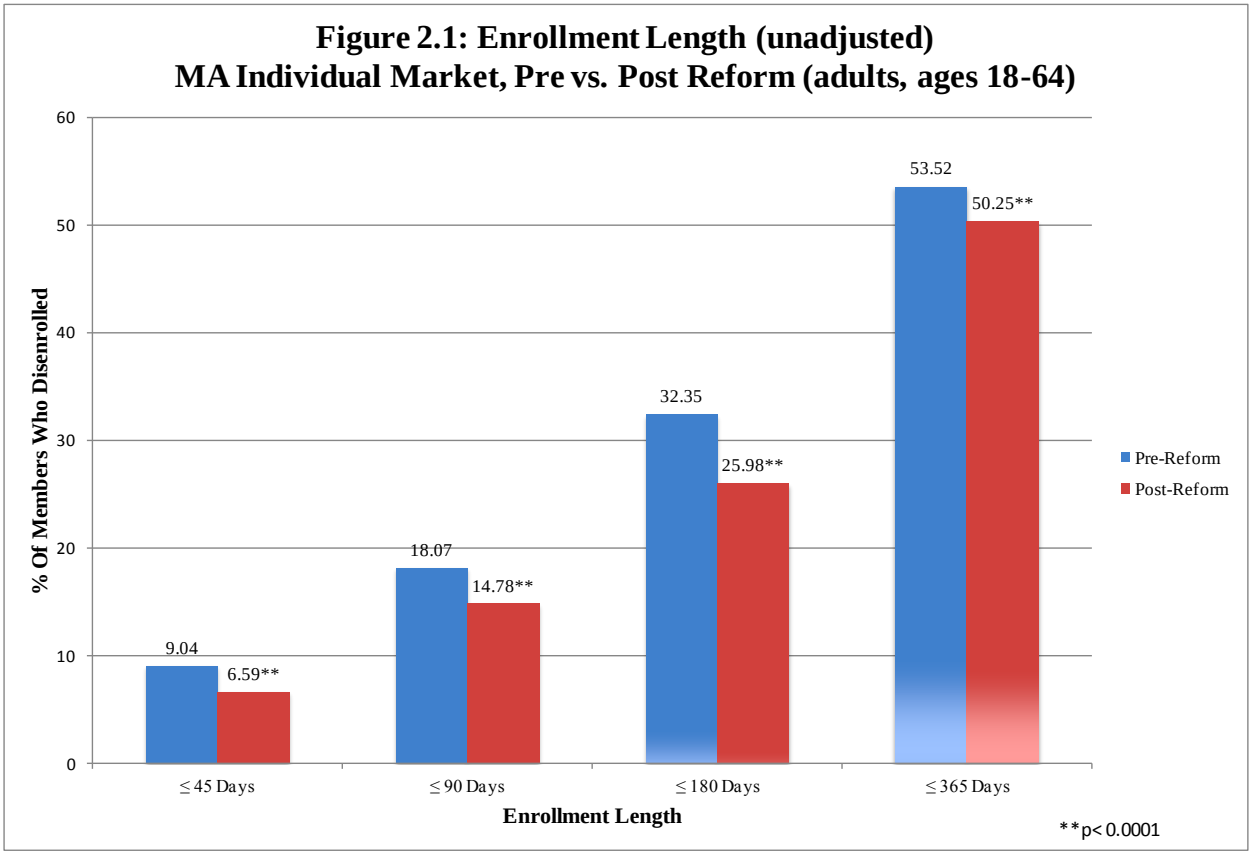
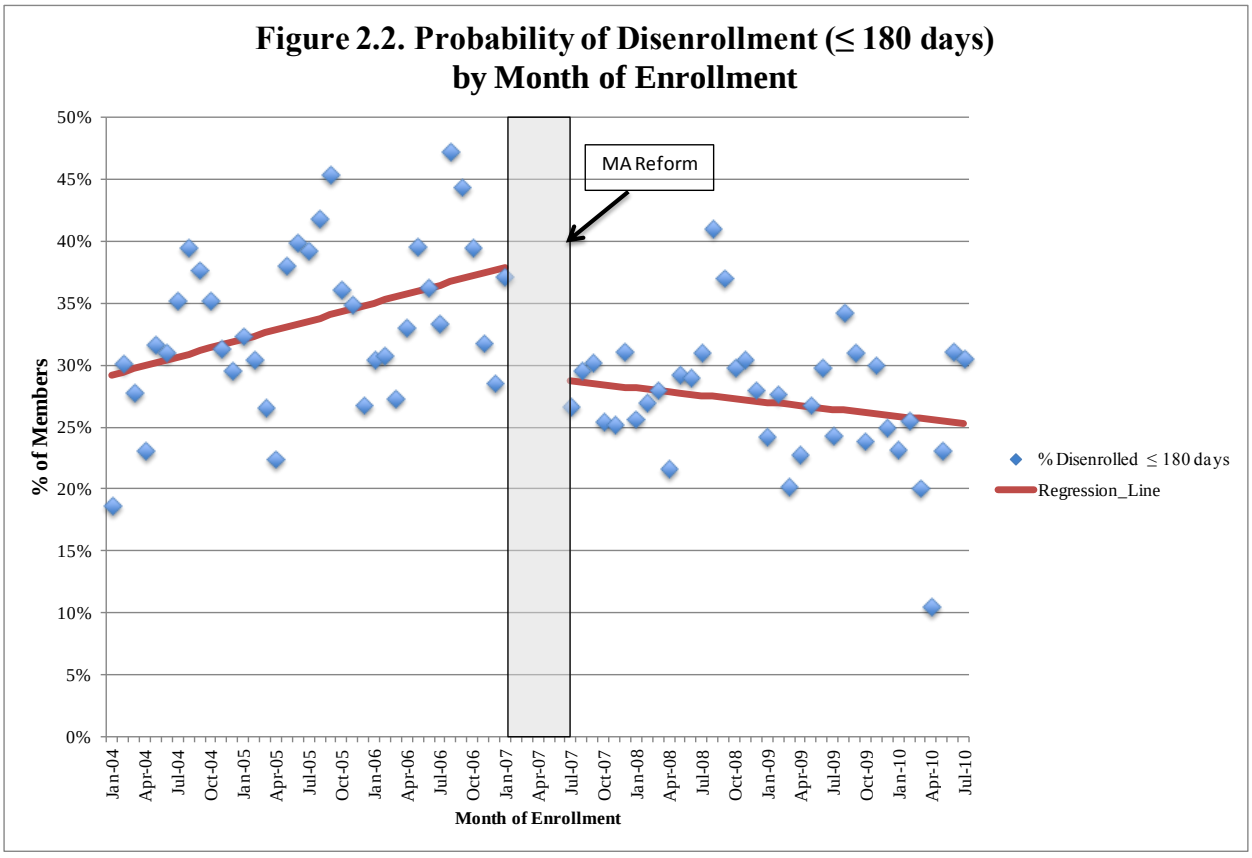


Table 2.2: Segmented Regression Models: Probability of Disenrollment by Month of Enrollment

Enrollment Length	Immediate Post-Reform Level Change[a] (std. err.)
≤ 45 days	-4.54 (1.15)*
≤ 90 days	-5.26 (1.83)*
≤ 180 days	-10.35 (2.96)*
≤ 1 year	-7.50 (2.99)*

[a] Percentage point change



The reform was a significant predictor of time to disenrollment in unadjusted and adjusted survival analyses [Table 2.3, Appendix 2 Figure 1 and Table 3]. The rate of disenrollment was significantly lower in the post-reform period (HR=0.811, 95% CI: 0.784,0.838) when controlling for demographic and plan characteristics [Table 2.3]. Interactions with the reform and age,

education, race, and plan type (individual/family plan) were significant [Appendix 2 Table 3], so we stratified the model by these variables. While all stratified groups had lower rates of disenrollment in the post-reform period, members who were older, in family plans, and live in areas with higher college attainment and percentage of white, non-hispanic residents had greater reductions in the rate of short-term enrollment following the reform [Appendix 2 Table 4]. The enrollment length results did not change in the sensitivity analyses with the one-year follow-up period or with shorter allowable gap between enrollment periods (i.e., 45 days).

Table 2.3. Cox Proportional Hazard Models: Time to Disenrollment and First Medical Encounter, Pre vs. Post Reform

Outcome[a]	Post (vs. Pre) Reform Hazard Ratio (95% CI)
Disenrollment	**0.811 (0.784, 0.838)***
Encounter Type	
Ambulatory	**1.037 (1.004, 1.070)***
Emergency Department	**0.851 (0.795, 0.911)***
Inpatient	**0.830 (0.744, 0.927)***
Same Day Surgery	0.951 (0.842, 1.073)
Knee Surgery	0.846 (0.600, 1.194)
Infertility Treatment[b]	**1.697 (1.325, 2.174)***

[a] Models control for: sex, age, education, race, family income, and individual/family plan. Follow-up time = 3.5 years max in pre and post.
[b] Infertility treatment analysis limited to females ages 27-50.
*Wald $p<0.05$

Health Services Utilization

The rates of inpatient (HR=0.830, 95% CI: 0.744, 0.927) and emergency department (HR=0.851, 95% CI: 0.795, 0.911) encounters were significantly lower in the post-reform period in both the unadjusted and adjusted models [Table 2.3, Appendix 2 Table 5], suggesting that individual market members were less likely to have these types of encounters after the reform. Post-reform members had a slightly higher rate of ambulatory encounters (HR=1.037, 95% CI: 1.004, 1.070). The reform was not a significant predictor of time to same-day surgery encounter. Age and

income interactions were significant, [Appendix 2 Table 6] so we stratified the analyses by these variables. The higher ambulatory encounter rates following the reform were driven by members ages 27-50 and members from higher income areas, the lower emergency department rates were driven by members from higher income areas, and the lower inpatient encounter rates were driven by younger (i.e., ages 18-40) members and members from higher income areas [Appendix 2 Table 7].

For the elective procedures, the reform was not a significant predictor of time to arthroscopic knee surgery but was a predictor of infertility treatment (HR=1.697, 95% CI: 1.325, 2.174) [Table 3, Appendix 2 Table 8]. Interactions with plan type were significant [Appendix 2 Table 9] – the post-reform increase in the rate of infertility treatment was driven by members in individual, and not family, plans [Appendix 2 Table 6].

Discussion

Contrary to previous unpublished and anecdotal reports,[11-13] we did not find evidence that the MA health reform led to an increase in short-term enrollment in the unsubsidized individual insurance market. Our results suggest the opposite – the rate of short-term enrollment was higher in the pre-reform than in the post-reform period.

We also did not find consistent evidence of a post-reform increase in utilization. The rate of hospitalization and emergency department visits was actually *lower* in the post-reform period, but rate of ambulatory care was slightly higher. Overall, this suggests that the post-reform individual market members were, on average, healthier than the pre-reform members, which was

one aim of the insurance mandate. We found no evidence of an increase in arthroscopic surgery, but did see evidence of an increase in fertility treatments.

These results make sense given that pre-reform individual market plans were relatively more expensive[10] and adverse selection was more likely to occur before the reform.[18] Before the insurance mandate, MA had already implemented a policy of community rating and guarantee issue,[10,19] which meant that a person could not be charged higher premiums or denied coverage on the basis of pre-existing conditions before the reform. The reform changed two things - it made individual coverage less expensive[10,19] and mandated that everyone have insurance or pay a fine. With the relatively high price of insurance and no financial penalty for being uninsured, people in the pre-reform period had a greater incentive to enroll only when they were sick and disenroll if the cost of insurance outweighed the benefit. Our analyses, and previous analyses on the subsidized individual market in MA,[8,10] suggest that the individual mandate succeeded in attracting a relatively younger and healthier population into the individual market risk pool. And, it appears that more affordable coverage plus the mandate encouraged people to stay insured for longer periods of time.

Potential Market Failures

The evidence that post-reform members were less likely than pre-reform members to have inpatient or emergency department encounters suggests that the MA health reform, as intended, actually reduced adverse selection in the overall individual market. However, we did find evidence that suggests that some types of adverse selection may still occur. The reform was associated with increased use of infertility treatments. The Connector plan premiums are

considerably lower than the estimated cost of in vitro fertilization, which can exceed $12,400.[20] It is speculated that women employed by self-insured companies not subject to state laws that mandate insurance coverage of infertility treatment,[21] may have joined Connector plans to obtain coverage for infertility services, and then dropped individual market coverage after treatment. Our results corroborate this theory - we observed a post-reform increase in infertility treatment only among women who were the sole enrollee in their insurance plan. However, the number of women undergoing infertility treatment is small and is unlikely to have an impact on the entire individual market.

Although the reform reduced short-term enrollment, the high rates of disenrollment in the individual market may be cause for concern. The high rate of churning (i.e., individuals enrolling and then terminating coverage) could be indicative of rational consumer behavior, such as obtaining coverage during a short spell of uninsurance (i.e., between jobs) or switching to a more appropriate, less-costly insurance product. But this situation is not ideal - there is an administrative burden associated with each enrollment period. Whether or not this negatively impacts insurers depends on the relative cost of the premiums paid vs. the administrative costs of enrollment.

Comparison to Prior Research

Unlike previous reports,[11] we did not find an increase in short-term enrollment. There are multiple possible explanations. First, our sample included members enrolled over a 7-year period (3.5 years before and 3.5 years after the reform) whereas the earlier report only looked at enrollment at two points in time - 2006 and 2008. Second, we used different and more robust

analytic methods. Third, we had access to granular enrollment record data that allowed us to collapse multiple enrollment entries per member into a period of continuous enrollment, allowing for plan changes and short gaps in enrollment consistent with state insurance rules. It is not clear if or how the earlier report accounted for multiple enrollment records per member. During our study period, post-reform members had more enrollment records per person than pre-reform members and the average length of the first enrollment period was shorter in post-reform period (data not shown). But, when we collapsed these enrollment records into periods of continuous coverage, short-term enrollment did not increase in the post-reform period.

Consistent with our findings that the rates of hospital and emergency department utilization were lower in the post-reform period, the report found that per member per month (PMPM) claims costs in the individual market declined from 2006 to 2008 for all durations of coverage, even for short-term enrollees.[11]

Limitations and Future Research

This paper provides important new information on the impact of the MA reform on short-term enrollment and adverse selection in the individual market. However, there are multiple limitations and further research is needed. We analyzed data from a single insurer, and it is possible findings will vary by insurer - future studies should use these methods with data from other Massachusetts insurers. Our study focused on the unsubsidized individual market, additional worked should examine the extent of short-term enrollment and adverse selection in the subsidized individual market (i.e., Commonwealth Care plans).

Future research should target observed member behavior, including initial plan choice and plan switching. We limited our analysis to the individual market and we could not follow members once they left the HPHC system. However, even within HPHC, there was considerable switching between markets, particularly in the pre-reform cohort. Nearly half (42%) of individual market members in the pre-reform cohort and a quarter (26%) in the post-reform cohort were in a non-individual market HPHC plan immediately (i.e., within the 62 day enrollment window) prior to their individual market enrollment. Members with previous enrollment drove the post-reform reduction we observed in short-term enrollment (data not shown). Future work should examine the transitions between individual and group markets and look at churning within HPHC individual market plans to assess whether adverse selection occurs within an insurer's own products – we would expect sicker members to opt for plans with more comprehensive coverage (e.g., PPOs) over plans with more limited coverage and higher out-of-pocket payments (e.g., HMOs and HDHPs).[9]

The data used in our study have certain limitations. The data do not allow us to link dependents with the primary subscriber, so we cannot determine whether enrollment decisions of an entire family are driven by the health needs of one family member. And, since our only source of health information is utilization that occurred after enrollment into a HPHC plan, we are unable to measure, or control for, members' baseline health. This is a problem with all enrollment studies – methods to assess baseline health in these types of studies need to be established.

We were unable to control for unobserved differences that may affect disenrollment decisions and utilization, most importantly, prior health status. However, this is not important from a

policy perspective for two reasons. First, our analysis mimics reality – due to informational asymmetries, insurers must rely only on demographic and plan characteristics to predict disenrollment and utilization. And second, controlling for prior health status would lead us to underestimate adverse selection, which was one of our main study outcomes.

A major limitation of the paper was the lack of a comparator group. Using other states as a control group would allow us to control for potential confounders, such as secular trends, but HPHC does not serve the individual market in other states. Thus, we were unable to control for potential impacts of the 2008 economic recession, which started shortly after the MA reform. However, our unadjusted interrupted time series results suggest that short-term enrollment decreased immediately following the reform in July 2007, and prior to the recession (Appendix 2 Figure 2). And, post-reform trend changes, which may have been impacted by the recession, were small or non-significant. Future studies can also use the small group market, whose members do not make individual insurance exit and entry decisions, as a comparison group to control for secular trends.

Policy Implications

The authors of the earlier unpublished report recommended that, "consideration should be given to creating pre-existing condition provisions, waiting periods, or open enrollment periods"[11] and as a result, the MA legislature approved a law that restricts open enrollment in the individual market to two times a year in 2011 and once a year thereafter.[22] Given that we did not find an increase in short-term enrollment or adverse selection – the two potential problems that the open enrollment legislation was intended to address - the costs and benefits of this policy deserve

attention. It is important to assess potential unintended consequences of the open enrollment rules on accessibility of insurance in MA, especially since the national reform includes similar open enrollment restrictions.

Results from Massachusetts may not be generalizable to other states since the state's pre-reform economic and health insurance situation were unique.[23] Nevertheless, MA provides the best evidence of how the national reform will play out and the rest of the nation is closely scrutinizing the MA experience. The findings from the initial non-peer-reviewed report on short-term, high cost enrollment in MA,[11] called into question by our study, have received national media attention and have been cited by opponents of the reform.[24,25] It is crucial that evidence about the MA experience is accurate. Our results provide important lessons for other states and the Federal government as they implement the national health insurance reform.

REFERENCES

1 McDonough JE, Rosman B, Phelps F, Shannon M. The third wave of Massachusetts health care access reform. *Health Aff (Millwood).* 2006;25(6):w420–431.

2 Massachusetts Health Connector. Accessed on Dec 13, 2012. Available at: https://www.mahealthconnector.org/portal/site/connector.

3 Lischko AM, Bachman SS, Vangeli A. The Massachusetts Commonwealth Health Insurance Connector: Structure and Functions. The Commonwealth Fund. May 2009. Accessed on February 14, 2013. Available at: http://www.commonwealthfund.org/Publications/Issue-Briefs/2009/May/The-Massachusetts-Commonwealth-Health-Insurance-Connector.aspx.

4 PPACA. Accessed on Dec 13, 2012. Available at: http://www.healthcare.gov/law/index.html.

5 Kaiser Family Foundation. Summary of New Health Reform Law. 2011. Accessed on Dec 13, 2012. Available at: http://www.kff.org/healthreform/upload/8061.pdf.

6 Kaiser Family Foundation. Implementation Timeline. Accessed on Dec 13, 2012. Available at: http://healthreform.kff.org/timeline.aspx.

7 Akerlof G. The Market for 'Lemons': Quality Uncertainty and the Market Mechanism. *Quarterly Journal of Economics*. 1970; 84:237-249.

8 Chandra A, Gruber J, McKnight R. The importance of the individual mandate--evidence from Massachusetts. *N. Engl. J. Med.* 2011;364(4):293–295.

9 Cutler DM, Reber SJ. Paying for health insurance: The trade-off between competition and adverse selection. *The Quarterly Journal of Economics.* May 1998.

10 Blue Cross Blue Shield Foundation of Massachusetts. Massachusetts Health Reform: A Five-Year Progress Report. November, 2011. Accessed December 13, 2012. Available at: https://www.mahealthconnector.org/portal/binary/com.epicentric.contentmanagement.servlet.ContentDeliveryServlet/Health Care Reform/Overview/BlueCrossFoundation5YearRpt.pdf

11 Oliver Wyman (Dianna K. Welch and Kurt Giesa). June 2010. *Report to the Health Care Access Bureau with in the MA Division of Insurance: Analysis of individual health insurance coverage in MA before July 1, 2007 merger of small group and nongroup health insurance markets.* Accessed December 13, 2012. Available at:. http://www.mass.gov/Eoca/docs/doi/Companies/adverse_selection_report.pdf

12 Boston Globe (Kay Lazar). April 4, 2010. *Short-term customers boosting health costs: Lessons for US overhaul in gaming of Mass. System.* Accessed December 13, 2012. Available at: http://www.boston.com/news/health/articles/2010/04/04/short_term_customers_boosting_health_costs/

13 Boston Globe (Kay Lazar). June 30, 2010. *Short-term insurance buyers drive up cost in Mass.: Lawmakers look to close loopholes.* Accessed December 13, 2012. Available at: http://www.boston.com/news/local/massachusetts/articles/2010/06/30/short_term_insurance_buyers_drive_up_cost_in_mass/

14 Breyer F, Bundorf MK, Pauly MV. Health Care Spending Risk, Health Insurance, and Payment to Health Plans. Handbook of Health Economics. (Edited by Pauly MV, McGuire TG, Barros PP.). Volume 2, Pages 1-1126 (2011).

15 Center for Studying Health System Change. *Community Report: State Reform Dominates Boston Health Care Market.* September 2010. Accessed February 2, 2013. Available at: http://www.hschange.com/CONTENT/1145/1145.pdf

16 MA Health Connector. *Limits on health plan enrollment.* Accessed on December 14, 2012. Available at: https://www.mahealthconnector.org/portal/binary/com.epicentric.contentmanagement.servlet.ContentDeliveryServlet/FindInsurance/LimitedEnrollmentNotice/LimitedOEFactSheet.pdf

17 Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther*. 2002;27(4):299-309.

18 Hackmann MB, Kolstad JT, Kowalski AE. Health Reform, Health Insurance, and Selection: Estimating Selection into Health Insurance Using the Massachusetts Health Reform. *American Economic Review: Papers & Proceedings* 2012, 102(3): 498–501. Accessed on December 14, 2012. Available at: http://www.econ.yale.edu/~ak669/aer.102.3.498.pdf (May 2012 version) and http://www.nber.org/papers/w17748 (January 2012 version)

19 Doonan MT, Tull KR. Health care reform in Massachusetts: implementation of coverage expansions and a health insurance mandate. *Milbank Q*. 2010;88(1):54–80.

20 American Society for Reproductive Medicine. *Frequently Asked Questions About Infertility.* Accessed on February 14, 2013. Available at: http://www.asrm.org/awards/index.aspx?id=3012

21 Massachusetts General Laws 175 § 47H. Accessed on February 14, 2013. Available at: http://www.malegislature.gov/Laws/GeneralLaws/PartI/TitleXXII/Chapter175/Section47H.

22 Governor Deval Patrick, Press Release. *Governor Patrick Signs Legislation to Reduce Health Care Costs for Small Businesses.* August 10, 2010. Accessed on December 14, 2012. Available at: http://www.mass.gov/?pageID=gov3pressrelease&L=1&L0=Home&sid=Agov3&b=pressrelease&f=100810_Small_Biz_Healthcare&csid=Agov3

23 Joyce TJ, Holtz-Eakin D, Gruber J. Point/counterpoint: what can Massachusetts teach us about national health insurance reform? *J Policy Anal Manage*. 2010;30(1):177–195.

24 New York Times (Robert Pear). August 2, 2010. *Covering new ground in health system shift.* Accessed on December 14, 2012. Available at: http://www.nytimes.com/2010/08/03/health/policy/03insurance.html?_r=1&

25 The Wall Street Journal (Grace-Marie Turner). November 9, 2011. *ObamaCare: Flawed Policy, Flawed Law: Even if it were to survive the high court's judgment, the individual mandate would never work as the law's drafters intended.* Accessed on December 14, 2012. Available at: http://professional.wsj.com/article/SB10001424052970204190704577024322624284592-lMyQjAxMTAxMDAwOTEwNDkyWj.html?mod=wsj_share_email&_nocache=1350934762117&user=welcome&mg=id-wsj&mg=reno64-wsj

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Chapter 3: The Invalidity of the Most Common Instrumental Variable Analyses in Comparative Effectiveness Research [e,f]

[e] This chapter was co-authored by Stephen Soumerai, Alan Zaslavsky, Darren Toh and Paula Chu.

[f] This project received ethics approval from the Harvard Pilgrim Health Care Institute Office of Sponsored Programs.

ABSTRACT

Context: Comparative effectiveness research (CER) relies heavily on observational methods to estimate treatment effects to guide clinical and regulatory decisions. Instrumental variable (IV) analysis is an increasingly popular CER approach that relies on identification of a variable (the IV) that affects treatment assignment but does not otherwise affect outcomes. In theory, the approach mimics random treatment assignment seen in randomized trials. In practical application, however, the analysis may be biased if the IV and the outcome are related through an unadjusted third variable ("IV-outcome confounder"), leading to questionable findings.

Objective: To evaluate trends in the use of IVs for CER and systematically identify the existence and impact of confounders of common IVs on study validity.

Design, Setting, and Participants: We conducted a systematic search in PubMed and other health/economic databases to identify published CER studies that use IV methods conducted in the US or other industrialized countries through 2011. We searched for evidence of potential confounders of the most common IV-outcome pairs.

Main Outcome Measures: Count of IV CER studies (by year, country, and outcome measure), major confounders of most common IV-outcome pairs, and proportion of IV CER studies that failed to control for these confounders.

Results: We found 187 IV CER studies meeting the selection criteria. Of these, 60.9% used one of the four most common IV categories – regional variation (26.2% of studies), distance to facility (20.3%), facility variation (11.8%), and physician variation (7.5%). Mortality was the most common outcome. We observed overwhelming evidence of IV-outcome confounding. Major confounders of the four most common IVs and mortality include patient's race, socioeconomic status, clinical risk factors, health status, and urban/rural residency, and facility

and procedure volume. Every IV CER study failed to control for one or more of these potentially major confounders.

Conclusions: Many effect estimates from IV analyses in CER may be biased by the failure to adjust for major IV-outcome confounders, which can lead to overestimation, underestimation or complete reversal of the true treatment effect. While no observational method can completely eliminate confounding, we caution against over-reliance on IV studies for CER.

Introduction

Patients, providers and payers are increasingly relying on comparative effectiveness research (CER), which compares the benefits and harms of alternative clinical and health care delivery methods,[1] to inform evidence-based health care decision-making. Because CER is intended to guide health care resource allocation, its validity is crucial. Since randomized controlled trials (RCTs) are not always feasible or generalizable, CER relies heavily on observational studies,[2,3] which are susceptible to confounding bias and other threats to validity.[4]

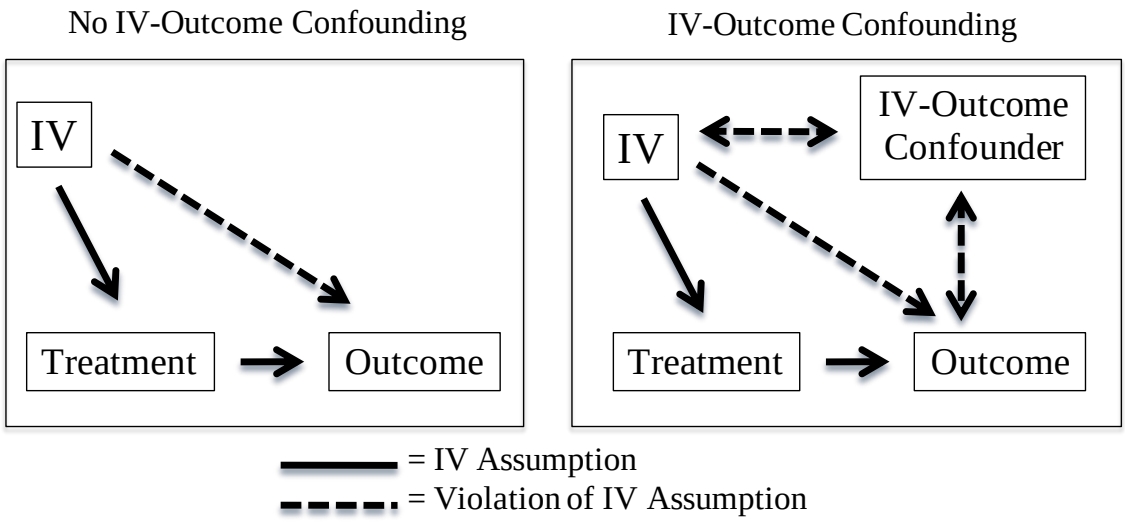
Instrumental variable (IV) analysis has been recommended as a method to establish causal conclusions from observational CER studies.[2,5-7] In theory, IVs induce variation in treatment assignment that allows causal inferences similar to those from a RCT [Figure 3.1]. While IV analysis is mathematically valid under certain assumptions, [5,8-15] it is difficult to implement in practice. In observational CER it is often challenging to identify an IV that meets all the assumptions required to make the analysis valid.

An example illustrates the IV method and its assumptions. Several studies have used relative distance to hospitals as an IV in analyses aimed at estimating the effects on mortality of treatment with invasive cardiac procedures, specifically cardiac catheterization, following a heart attack.[16-22] Researchers classify each hospital in the study region as a catheterization hospital or a non-catheterization hospital, based on the presence of a catheterization lab or the overall intensity (or volume) of catheterizations. Patients are assigned a value of the binary IV based on whether they live closer to a catheterization hospital, making them more likely to receive the procedure, or a non-catheterization hospital. This IV analysis assumes that, similar to random

assignment, the relative distance between a patient's residence and a cardiac catheterization hospital predicts treatment choice independently of all characteristics (e.g., age, socioeconomic status, health status or use of life-saving medications) that usually confound the relationship between treatment choice and outcome.

The IV method relies on two critical assumptions. One, the IV (relative distance to hospital) is predictive of treatment choice (use of cardiac catheterization). And two, the association between relative distance and mortality is due only to the effect of relative distance on treatment assignment, after control for observed variables [Figure 3.1]. Hence, IV estimates of treatment effects may be biased if relative distance is related to mortality directly or through an unadjusted third variable – an IV-outcome confounder. A plausible IV-outcome confounder is rural residence. Patients living in rural areas are more likely to live closer to a non-catheterization hospital, creating an association of the IV with rurality.[16] Furthermore, there is ample evidence that rural residence is associated with multiple risk factors for mortality.[23-25] Therefore, an IV analysis would likely overstate the effect of catheterization since patients in the control group are on average sicker and more likely to die.

Figure 3.1: Instrumental Variable Assumptions



The IV method substitutes actual random assignment to treatment with an IV, a variable that predicts treatment assignment but is not related to all other factors that influence the outcome. This method relies on two critical assumptions: (1) the IV is correlated with the actual treatment and (2) the association between the IV and the outcome is due only to the effect of the IV on treatment assignment, after control for observed variables. Hence, IV estimates of causal effects may be biased if the IV and outcome are directly related (i.e., violation of "exclusion restriction") or if the IV and the outcome are related through an unadjusted IV-outcome confounder.

Although IV methods have been recommended as a tool for CER using observational data, there is a consensus that more research on the validity of IV in CER is needed, particularly concerning violations of the second IV assumption.[2,5,26] To date there has been no critical systematic review to identify commonly used instrumental variables and assess the plausibility of the IV assumptions. While the second IV assumption is technically unverifiable, the identification of IV-outcome confounders through other sources provides evidence that an IV estimate may be biased. Few researchers go beyond their own, often limited, data to look for IV-outcome confounders.[26]

This is the first comprehensive review of the validity of IV methods used in CER. In this study, we review relevant literature to identify IVs in CER, evaluate trends in the use of IVs in

published CER studies, and identify the existence and potential impact of IV-outcome confounders for commonly used IVs. We provide the first published list of confounders that may compromise the validity of CER studies that use some of the most common IVs. We conclude by assessing the limitations and potential of IV in CER and recommending the use of CER methods that rely on assumptions that are more transparent and less likely to bias results.

Methods

Study Selection

We conducted a systematic review in PubMed, EconLit, PsychInfo, Social Services Abstracts, Social Sciences Citation Index, and Web of Science to identify IV CER studies that were published in an English-language, peer-reviewed journal through December 31, 2011 and conducted in the US and other industrialized countries. See Appendix 3.1 for specific search terms.

We used the Institute of Medicine's broad definition of CER that is inclusive of both patient-level clinical interventions and system-level health care policies.[1] We included non-interventional studies (e.g., a study on the association between school junk food exposure and obesity) if the topic was amenable to clinical interventions or policy changes and the study included health-related outcomes. We excluded studies that were purely methodological, used simulated data, or applied IV methods in a RCT. We also excluded studies that used Mendelian randomization as an IV to elucidate biological mechanisms of disease[27] and studies that used IV to adjust for the effects of measurement error.[28]

Analysis of IV CER Studies

We categorized all IV CER studies by year of publication, number of articles that cite the study, country, type of intervention, study population, type of IV, strength of IV, and outcome. We measured the trend in use of IVs in published studies of CER by year. We also identified the most commonly used IV-outcome pairs.

Identification of IV-Outcome Confounders

IV-outcome confounders (hereafter also referred to as "confounders") are variables that are related to both the IV and outcome of interest, conditional on measured covariates and the treatment assignment. IV-outcome confounders violate the causal inference assumption that the IV is independent of potential outcomes [29] and suggest that the IV is not equivalent to random assignment.[8] In our example, the confounder of rural residence is associated with numerous health and health care disadvantages that almost certainly affect clinical outcomes, regardless of treatment assignment, thus mediating an association between the relative distance IV and outcomes that does not pass through the treatment under study. For the purposes of this paper, we included as IV-outcome confounders variables that are directly causally related to the outcome (e.g., receipt of another lifesaving treatment) or that mediate the pathway between the IV and the outcome (e.g., risk factors for the outcome, such as rurality).

We employed multiple search strategies in PubMed and other databases to identify peer-reviewed articles that provided evidence of confounding for the most commonly used IV-outcome pairs. For example we searched for studies that included *both* IV and outcome to identify covariates that are potential confounders. We also used a two-step search strategy: we

searched for evidence of variables that are correlated with each IV, and then searched to determine if these variables are also correlated with the study outcome. See Appendix 3.2 for specific search terms and strategies.

We created a database of potential confounders for each IV-outcome pair that includes estimates, when available in the literature, of the size and direction of the IV-confounder relationship and the outcome-confounder relationship. We included univariate and multivariate (i.e., adjusted) estimates of association, with a preference for the latter.

We determined which confounders are likely to introduce the most bias, taking into account the probable direction and size of the bias and the extent of evidence in the literature. We re-reviewed the IV CER articles to determine what percent of studies controlled for these major confounders.

Analysis of Bias

We estimated the direction and size of the bias introduced by potential confounders. The asymptotic bias of the IV estimator with a single confounder can be obtained from a simple equation of the coefficients of three relationships [Figure 3.1]:

$$\text{Bias} = \text{outcome-confounder relationship} * \frac{\text{IV-confounder relationship}}{\text{IV-treatment relationship}}$$

See Brookhart et al. (2007) for a more technical explanation of the IV estimator and bias calculation.[30]

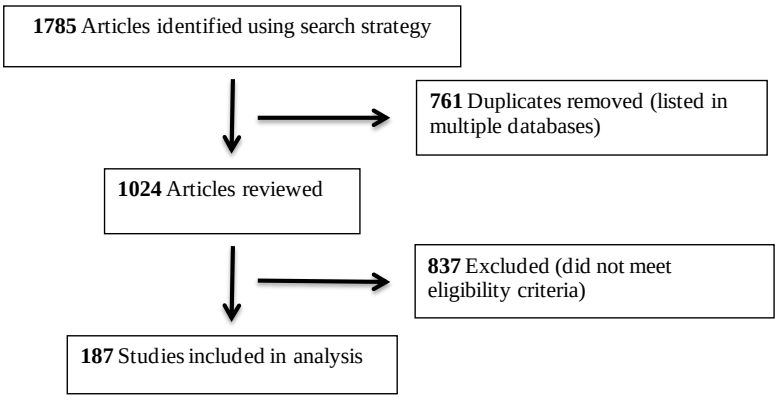
We determined the likely direction of the bias introduced by each confounder, which is the sign of the IV-confounder relationship multiplied by the sign of the outcome-confounder relationship (assuming the IV-treatment relationship is always positive). The interpretation of the bias is dependent on the direction of the treatment effect. We assume that a positive bias overstates the benefit of the treatment and a negative bias underestimates the treatment effect (i.e., biases towards the null). Since the size of the bias is study-specific, we measured bias in the context of one study to demonstrate how this analysis can be applied in practice (described in discussion section).

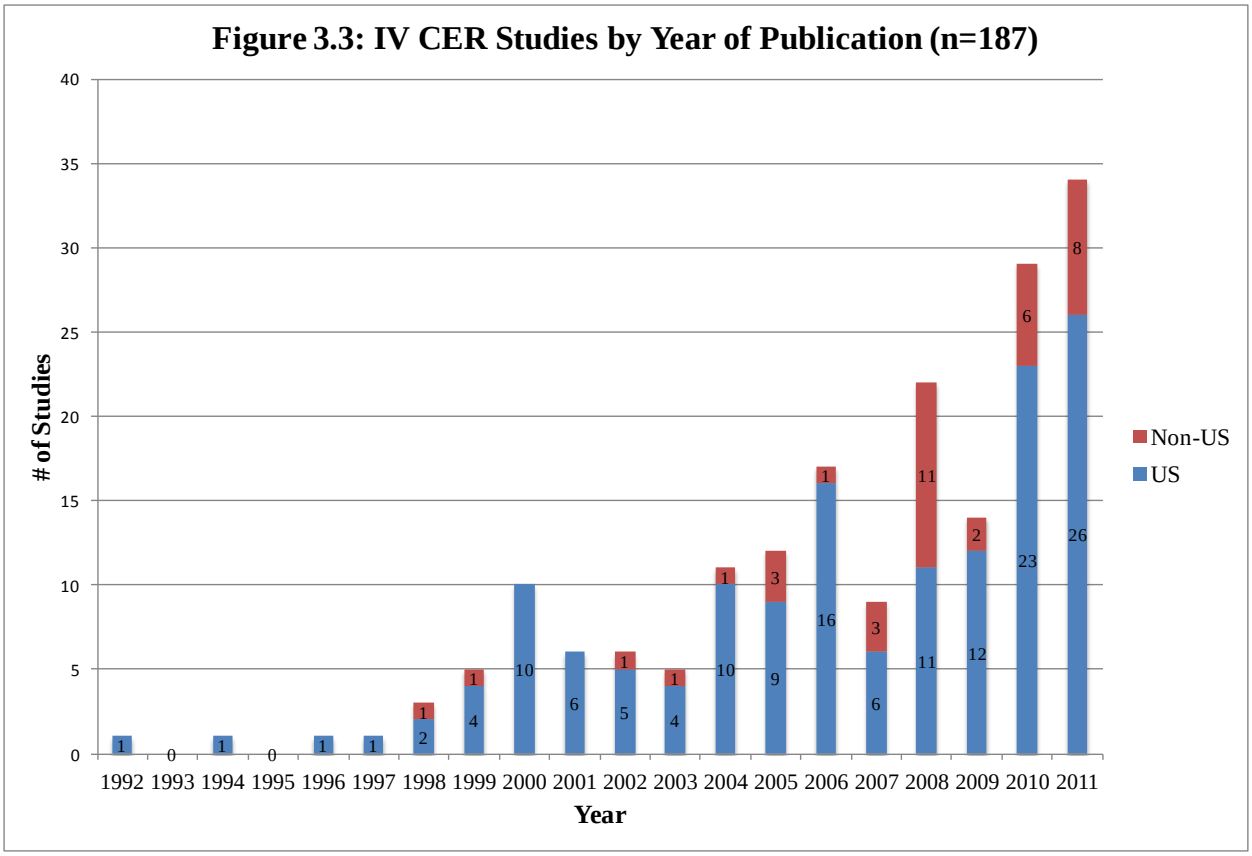
Results

Systematic Review

A total of 1,024 studies were reviewed and 187 met our eligibility criteria [Figure 3.2; see Appendix 3.3 for database of all IV CER studies]. Use of IV methods in CER studies has accelerated since the early 1990s [Figure 3.3], with a large spike in US-based studies in 2010 and 2011, likely due to increased federal funding for CER as part of the economic stimulus in 2009.[3]

Figure 3.2: Systematic Review Results





Over half (60.9%) of the IV CER studies used at least one of the four most common IV categories – regional variation (26.2% of studies), distance to facility (20.3%), facility variation (11.8%), and physician variation (7.5%) [Table 3.1, Appendix 3.4]. Mortality was the most common outcome for each of the top four IV categories [Appendix 3.4]. We focused on these most common IV-outcome pairs in the subsequent analyses.

Table 3.1: Description of the Four Most Commonly Used IV Categories

IV Category	Number of Studies [a]	How IV assigns to treatment status [b]	How IV defines treatment status [b]	Example of IV treatment assignment [b]
Distance to Facility	38 (20.3%)	Distance[c] from patient's residence to facility of interest [d]	Facility-level: high vs. low treatment rate, existence of specialty provider or unit, special designation (e.g., trauma, teaching)	Patient resides closer to a hospital with a high cardiac catheterization rate is assigned by IV as treated
Regional Variation	49 (26.2%)	Treatment patterns (e.g., local practice styles) in region[e] where patient lives or is treated	Region-level: high vs. low treatment rate, policies that impact practices in region, provider supply or market share	Patient resides in an area with a high cardiac catheterization rate is assigned by IV as treated
Facility Variation	22 (11.8%)	Treatment patterns (e.g., local practice styles) in facility where patient is treated[d]	Facility-level: high vs. low treatment rate, procedure volume, provision of specific services, indicator of quality measures	Patient is treated in hospital with a high cardiac catheterization rate is assigned by IV as treated
Provider Variation[f]	14 (7.5%)	Treatment patterns (e.g., preference) of treating physician	Physician-level: high vs. low treatment rate, most recent prior prescription in the therapeutic area to a new patient	Patient is treated by physician with a high cardiac catheterization rate is assigned by IV as treated

[a] Some studies used IVs from multiple categories and are therefore counted more than once. Percent is of 187 total IV-CER studies.

[b] The "treatment" referred to here is not actual receipt of the treatment. It refers to the IV assignment to the treatment group.

[c] Distance can be measured in absolute or relative terms and using various methods (e.g., straight line/Euclidian distance, travel time). Just over half (21 studies; 55.3%) of distance IVs used relative, or differential, distance to predict treatment (e.g., the distance from patient's home to a high procedure rate hospital minus the distance from a patient's home to a low procedure rate hospital). The rest of the studies used absolute distance (e.g., the distance to patient's home to high procedure hospital).

[d] Facility is often a hospital.

We found that while most (89%) IV CER studies in our sample assessed the strength of the IV [Appendix 3.3], there was wide variation in the strength of the IVs, and many IVs were weak predictors of actual treatment.

IV-Outcome Confounders

We found overwhelming evidence of IV-outcome confounders that call into question the validity of the IV CER studies' conclusions [Table 3.2, Appendix 3.5]. Major confounders of the four most-commonly used IVs and mortality include: patient's race, socioeconomic status, risk factors for mortality, health status, and urban/rural residency; and facility and procedure volume. Many other confounders are less researched but well recognized, such as factors associated with time-to-treatment (e.g., door- to-needle time), receipt of other treatments (e.g., lifesaving medications), and facility characteristics (e.g., teaching hospital status) that are associated with mortality.

Table 3.2: Confounders for Most Commonly Used IVs in CER and Mortality

IV Category	Confounder Category	Confounders[a]
Distance to Facility (e.g., Hospital)[b]		
	Geographical location	urban/rural; region of the US, absolute distance (for relative difference)
	Patient characteristics	race, education, income, age, insurance status, health status, comorbidities, health behaviors
	Treatment characteristics	receipt of other treatments, time-to-treatment, transfer status
	Facility characteristics	all "facility characteristics" confounders from facility variation below apply
Regional Variation		
	Geographical location	urban/rural; region of the US
	Patient characteristics	race, education, income, age, insurance status, health status, comorbidities, health behaviors
	Provider supply	number of hospital beds or nursing homes, procedure volume, facility volume
	Technology adoption and utilization	invasive cardiac procedures, radical prostatectomies, prescribing behavior, practice patterns
	Treatment characteristics	receipt of other treatments, time-to-treatment, transfer status
	Facility characteristics	all "facility characteristics" confounders from facility variation apply
Facility (e.g., Hospital) Variation		
	Geographical location	urban/rural
	Patient characteristics	race, education, income, age, insurance status, health status, comorbidities, health behaviors
	Facility characteristics	procedure volume, facility volume, clinical services offered, departments, teaching status, profit status, trauma designation, delivery system type, practice type
	Treatment characteristics	receipt of other treatments
Provider Variation		
	Physician characteristics	age, gender, specialty, board certification, physician volume
	Patient characteristics	race, education, income, age, insurance status, health status, comorbidities, health behaviors
	Treatment characteristics	receipt of other treatments
	Health system characteristics	reimbursement policies, all regional variation and facility variation confounders apply

[a] See Appendix 3.5 for list of references that provided evidence of confounding.
[b] These confounders are applicable to both absolute and relative distance IVs, unless noted otherwise.

Control for Confounding in Current Literature

We reviewed the studies that used one of the top four categories of IVs and had a mortality outcome to determine if the authors controlled for major confounders. All studies in our review failed to control for one or more of the major, identified confounders in Table 3.3 [see Appendix 3.6 for results by individual study]. While the majority of IV CER studies (by IV category) controlled for at least one patient health status variable and race, less than half of the studies in each IV category controlled for income, education, urban/rural location and volume [Table 3.3]. Notable exceptions appeared among regional variation IV studies: 70% controlled for patient income and 52% controlled for urban/rural location.

Table 3.3: Percent of Studies that Controlled for Major Confounders by IV Category[a]

	Instrumental Variable Category			
Confounders	**Distance (n=27 studies)**	**Regional Variation (n=23)**	**Facility Variation (n=14)**	**Physician Variation (n=8)**
Patient Race	77.78%	69.57%	78.57%	62.50%
Patient Income	40.74%	69.57%	14.29%	25.00%
Patient Education	11.11%	21.74%	14.29%	0.00%
Patient Co-morbidities/ health status	100.00%	82.61%	85.71%	100.00%
Urban/Rural (patient residence or facility location)	44.44%	52.17%	7.14%	12.50%
Volume (procedure)[b]	3.85%	0.00%	27.27%	12.50%
Volume (facility)[b]	40.74%	40.91%	38.46%	12.50%

[a] Analysis limited to studies that use one of the four most commonly-used IVs and a mortality outcome.
[b] We removed from the denominator studies that used procedure or facility volume as an IV or independent variable.

Direction of Bias

For most confounders, we found evidence that suggests either a positive or a negative bias, leading to an overestimation or underestimation of the treatment effect, respectively [Appendices

7-10]. It is difficult to make generalized statements about the direction of the bias introduced by confounders since the evidence is often mixed and context-dependent. Similarly, the size of the bias introduced by a confounder is study-specific and therefore difficult to generalize.

For instance, geography confounds all of the top four IVs, but the direction of bias is not clear. Patients living in urban areas are more likely to live closer to any health facility,[31-33] including a cardiac catheterization hospital,[16] than patients residing in rural areas. In the introduction, we provided a simplified example showing how relatively poor health in rural regions could cause a positive bias (i.e., overestimation of treatment effect). However, depending on the region of the country and study population, urban *or* rural residents (compared to suburban residents) have more risk factors for poor health and higher mortality.[23-25,32-42] In areas where rural mortality is relatively high, such as predominately white, low-income Appalachia,[23] a distance IV may overestimate the treatment effect since relatively healthier patients live closer to the hospital. Conversely, in areas where urban mortality is relatively high, such as high-density black cities,[23] a distance IV may underestimate the treatment effect since sicker patients live closer to the hospital.

For some confounders, the direction of the bias is more predictable. In many cases, the confounders cause an overestimation of the treatment effect since various forms of advantage are correlated with each other. For example, patients who live closer to a hospital – and are therefore assigned to the "treatment group" via a distance to hospital IV – are more likely to get the treatment of interest *and* receive other time-sensitive, life-saving treatments that improve survival.[43] Similarly, patients who receive one innovative treatment, such as cardiac catheterization, may be more likely to receive other aspects of high-quality care (e.g., in teaching

hospitals[44,45]). These confounders will result in an overestimation of the beneficial effect of the treatment – the confounded IV estimate incorrectly attributes the positive effect of the other treatments and aspects of care to the treatment of interest.

Conclusions

IV analysis is an increasingly popular method for CER. IVs are popular for CER since, unlike other statistical methods that control for observed confounders (e.g., propensity score), IVs *theoretically* control for both observed and *unobserved* confounders. However, it is likely that most effect estimates from IV analyses in observational CER studies are biased by the failure to adjust for IV-outcome confounders.

We found overwhelming evidence of confounders of the four most popular IVs that call into question the trustworthiness of the results of IV CER studies. The identification of IV-outcome confounders suggests that key IV assumptions are not often met and, therefore, in these cases, the IV method should not be used. We found it difficult to make general conclusions about the direction and size of the bias introduced by most confounders since the evidence was often conflicting and context-dependent. Thus, even the direction of the bias in any study may be hard to predict unless the confounder is measured in the study population. As we have shown, all 64 studies that used one of the four most popular IVs failed to adjust for one or more major confounders affecting mortality.

We demonstrated how to measure the direction and size of the bias introduced by a confounder using an example motivated by our review of the literature in Appendix 3.11. The degree of bias

was highly dependent on the direction and size of the confounder-IV and confounder-outcome relationships and the strength of the instrument (i.e., the relationship between the IV and the treatment of interest). A confounded IV can lead to overestimation, underestimation or complete reversal of the true treatment effect and a "weak" IV will inflate any residual bias. Additionally, the residual association between the IV and the treatment assignment may be greatly weakened if the IV-outcome confounders are measured and controlled for. For instance, the association between relative distance to a cardiac catheterization hospital and actual receipt of treatment might be much smaller if we control for rurality. If most rural residents live closer to a non-catheterization hospital and most urban residents live closer to a catheterization hospital, there will be less variation *within* each group (i.e., rural and urban populations), leaving little predictive value of the distance IV.

Some confounders have particularly high potential to introduce bias. For instance, geography, race and income are strongly linked to mortality:[24,25,33,46] in the US, the gap between race-county combinations with the highest and lowest life expectancies is over 35 years.[33] Our results showing that the most popular IVs in CER are correlated with these variables provide strong evidence of confounding.

The validity of IV analysis might be improved if IV-outcome confounders were measured and controlled for. However, all studies in our analysis failed to control for *one or more* major confounders. And, some confounders (e.g., race[47]) are difficult to measure. Controlling for inadequately measured confounders will still result in residual bias.

We encourage the use of multiple observational analytic methods to examine the robustness of IV study results. Many of the IV-CER studies used complementary approaches, such as adjusted regression and propensity score models. However, treatment-outcome confounding is an issue common to all observational methods used in CER. Many CER studies rely on electronic healthcare databases or databases that are not created for research purposes. These datasets often do not include information on important confounders, such as patient demographic and health system characteristics. More comprehensive data sources are needed for all observational CER studies, including systematic reviews of confounders in previous studies as in this report.

Our findings cast uncertainty about the validity of the most popular IVs used in CER. However, confounding is generally not an issue when the instrument is random assignment, as is the case with randomized encouragement designs (e.g., IV is a randomized reminder sent to physicians to offer the flu shot). The IV estimator can be used with the most confidence when the encouragement is truly randomized and also with some confidence when the encouragement is introduced through a policy (differing over place, time or population subgroup) that can be reasonably regarded as exogenous. Yet, randomized encouragement and policy change IVs may be weak instruments (i.e., few "encouraged" patients actually receive treatment or physicians ignore the reminders) since they often rely on behavior change and patient compliance.

There are several limitations to this study, all of which were created by our attempts to maintain a feasible study scope. First, our search was not intended to produce an exhaustive list of all potential IV-outcome confounders, nor of all studies that provide empirical evidence in support of each confounder. Our list of confounders is likely the "tip of the iceberg," resulting in an

under-estimation of bias in IV studies. Second, we limited our confounder search to the most common IV categories and therefore do not provide evidence regarding confounders for the other IVs. Third, the studies that we cite as evidence of confounders include cross-sectional studies of association that do not control for all possible confounders. However, for our purposes, exact estimates of bias due to each confounder were less important than knowing that confounding was present. Moreover, it is likely that a confounded estimate is actually measuring the joint impact of the confounder and other unmeasured variables, which would also qualify as confounders (e.g., the confounder of race is also measuring income and education). Finally, the impact of a confounder, if any, is study-specific and depends on the definition of the IV, the other variables that are controlled for in the model, the intervention, and the patient population. The IV-outcome associations we identified may also not be generalizable to all IV CER studies. Our goal was to provide general evidence of potential confounders and to demonstrate how these confounders could bias the results. It is the responsibility of researchers to assess confounding in specific IV studies.[7]

In conclusion, we have observed that the use of IV in CER is often a reaction to limited resources and data availability. In this case, the questionable validity of popular IVs in CER suggests that IV analysis may produce inaccurate information for evidence-based decision-making in health care. While no observational method can completely eliminate confounding, we found that most IV CER studies are over-confident in assuming that confounding is not present and we believe that IVs should be used rarely in CER because their results are often biased. We recommend approaches that better control for confounding and other biases, such as

experimental and other quasi-experimental designs,[4] in order to generate valid CER evidence to support more rational allocation of medical resources.

REFERENCES

1 Institute of Medicine. *Initial Priorities for Comparative Effectiveness Research*, 30 June 2009. Available at: http://www.iom.edu/Reports/2009/ComparativeEffectivenessResearchPriorities.aspx. Accessed 31 January 2011.

2 Tunis SR, Benner J, McClellan M. Comparative effectiveness research: Policy context, methods development and research infrastructure. *Stat Med*. 2010;29(19):1963-1976.

3 Garber AM. How The Patient-Centered Outcomes Research Institute Can Best Influence Real-World Health Care Decision Making. *Health Aff*. 2011;30(12):2243–2251.

4 Shadish WR , Cook TD, Campbell DT. Experimental and Quasi-Experimental Designs for Generalized Causal Inference. Houghton Mifflin; Boston, MA: 2002. Chapter 6-7.

5 Brookhart MA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. *Pharmacoepidemiol Drug Saf*. 2010;19(6):537-554.

6 Johnson ML, Crown W, Martin BC, Dormuth CR, Siebert U. Good research practices for comparative effectiveness research: analytic methods to improve causal inference from nonrandomized studies of treatment effects using secondary data sources: the ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report--Part III. *Value Health*. 2009;12(8):1062-1073.

7 Patient-Centered Outcomes Research Institute. *PCORI Methodology Standards*. December 14, 2013. Accessed on February 14, 2013. Available at: http://www.pcori.org/assets/PCORI-Methodology-Standards.pdf.

8 Angrist JD, Pischke JS. *Mostly Harmless Econometrics: An Empiricist's Companion.* Princeton NJ: Princeton University Press; 2009

9 Wooldridge JM. *Introductory Econometrics: A Modern Approach.* 3rd edition. USA: Thomson;2006

10 Newhouse JP, McClellan M. Econometrics in outcomes research: the use of instrumental variables. Annu Rev Public Health 1998;19:17–34

11 Greenland S. An introduction to instrumental variables for epidemiologists. Int J Epidemiol 2000;29:722–729.

12 Martens EP, Pestman WR, de Boer A, Belitser SV, Klungel OH. Instrumental variables: application and limitations. Epidemiology 2006;17:260–267.

13 Glymour, MM. Natural experiments and instrumental variable analyses in social epidemiology. In: Oakes, JM.; Kaufman, JS., editors. Methods in Social Epidemiology. John Wiley and Sons; San Francisco, CA: 2006. p. 429-468.

14 Hernan MA, Robins JM. Instruments for causal inference: an epidemiologist's dream? Epidemiology 2006;17:360–372.

15 Grootendorst P. A review of instrumental variables estimation of treatment effects in the applied health sciences. Health Serv Outcomes Res Methodol 2007;10:159–179.

16 McClellan M, McNeil BJ, Newhouse JP. Does more intensive treatment of acute myocardial infarction in the elderly reduce mortality? Analysis using instrumental variables. JAMA. 1994;272(11):859–866.

17 McClellan M. Are the returns to technological change in health care declining? Proc. Natl. Acad. Sci. U.S.A. 1996;93(23):12701–12708.

18 Brooks JM, McClellan M, Wong HS. The marginal benefits of invasive treatments for acute myocardial infarction: does insurance coverage matter? Inquiry. 2000;37(1):75–90.

19 Glickman M, Normand S. The derivation of a latent threshold instrumental variables model. Statistica Sinica. 2000;10(2):517-544.

20 Beck CA, Penrod J, Gyorkos TW, Shapiro S, Pilote L. Does aggressive care following acute myocardial infarction reduce mortality? Analysis with instrumental variables to compare effectiveness in Canadian and United States patient populations. Health Serv Res. 2003;38(6 Pt 1):1423–1440.

21 Cutler DM. The lifetime costs and benefits of medical technology. J Health Econ. 2007;26(6):1081–1100. (Note: evaluation of revascularization only, not cardiac catheterization)

22 Pilote L, Beck CA, Eisenberg MJ, et al. Comparing invasive and noninvasive management strategies for acute myocardial infarction using administrative databases. Am. Heart J. 2008;155(1):42–48.

23 Murray CJL, Kulkarni SC, Michaud C, et al. Eight Americas: investigating mortality disparities across races, counties, and race-counties in the United States. *PLoS Med.* 2006;3(9):e260.

24 Cosby AG, Neaves TT, Cossman RE, et al. Preliminary evidence for an emerging nonmetropolitan mortality penalty in the United States. *Am J Public Health*. 2008;98(8):1470–1472.

25 Cossman JS, James WL, Cosby AG, Cossman RE. Underlying causes of the emerging nonmetropolitan mortality penalty. *Am J Public Health*. 2010;100(8):1417–1419.

26 Chen Y, Briesacher BA. Use of instrumental variable in prescription drug research with observational data: a systematic review. *J Clin Epidemiol*. 2011;64(6):687-700.

27 Didelez V, Sheehan N. Mendelian randomization as an instrumental variable approach to causal inference. *Stat Methods Med Res*. 2007;16(4):309–330.

28 Hu Y, Schennach SM. Instrumental Variable Treatment of Nonclassical Measurement Error Models. *Econometrica*. 2008;76(1):195-216.

29 Little RJ, Rubin DB. Causal effects in clinical and epidemiological studies via potential outcomes: Concepts and analytical approaches. *Annu. Rev. Public Health*. 2000;21:121–45.

30 Brookhart MA, Schneeweiss S. Preference-based instrumental variable methods for the estimation of treatment effects: assessing validity and interpreting results. *Int J Biostat*. 2007;3(1):14.

31 Abrams TE, Vaughan-Sarrazin M, Fan VS, Kaboli PJ. Geographic isolation and the risk for chronic obstructive pulmonary disease-related mortality: a cohort study. Ann. Intern. Med. 2011;155(2):80–86.

32 Khan JA, Casper M, Asimos AW, et al. Geographic and sociodemographic disparities in drive times to Joint Commission-certified primary stroke centers in North Carolina, South Carolina, and Georgia. Prev Chronic Dis. 2011;8(4):A79

33 Mackenzie TA, Wallace AE, Weeks WB. Impact of rural residence on survival of male veterans affairs patients after age 65. J Rural Health. 2010;26(4):318–324.

34 Murray CJL, Kulkarni SC, Michaud C, et al. Eight Americas: investigating mortality disparities across races, counties, and race-counties in the United States. *PLoS Med.* 2006;3(9):e260.

35 Baldwin L-M, MacLehose RF, Hart LG, et al. Quality of care for acute myocardial infarction in rural and urban US hospitals. J Rural Health. 2004;20(2):99–108.

36 Bradley EH, Herrin J, Curry L, et al. Variation in hospital mortality rates for patients with acute myocardial infarction. Am. J. Cardiol. 2010;106(8):1108–1112.

37 Cossman JS, Cossman RE, James WL, et al. Persistent clusters of mortality in the United States. Am J Public Health. 2007;97(12):2148-2150.

38 Culica D, Aday LA. Factors associated with hospital mortality in traumatic injuries: incentive for trauma care integration. Public Health. 2008;122(3):285–296.

39 Frances CD, Shlipak MG, Noguchi H, Heidenreich PA, McClellan M. Does physician specialty affect the survival of elderly patients with myocardial infarction? Health Serv Res. 2000;35(5):1093-116.

40 Galandiuk S, Mahid SS, Polk HC Jr, et al. Differences and similarities between rural and urban operations. Surgery. 2006;140(4):589–596.

41 Hutt E, Elder SJ, Fish R, Min S-J. Regional variation in mortality and subsequent hospitalization of nursing residents with heart failure. J Am Med Dir Assoc. 2011;12(8):595-601.

42 Loberiza FR Jr, Cannon AJ, Weisenburger DD, et al. Survival disparities in patients with lymphoma according to place of residence and treatment provider: a population-based study. J. Clin. Oncol. 2009;27(32):5376–5382.

43 Willison DJ, Soumerai SB, Palmer RH. Association of physician and hospital volume with use of aspirin and reperfusion therapy in acute myocardial infarction. Med Care. 2000;38(11):1092-1102.

44 Ayanian JZ, Weissman JS. Teaching hospitals and quality of care: a review of the literature. Milbank Q. 2002;80(3):569-593.

45 Hayanga AJ, Mukherjee D, Chang D, et al. Teaching hospital status and operative mortality in the United States: tipping point in the volume-outcome relationship following colon resections? Arch Surg. 2010;145(4):346–350.

46 Geronimus AT, Bound J, Colen CG. Excess black mortality in the United States and in selected black and white high-poverty areas, 1980-2000. *Am J Public Health*. 2011;101(4):720–729.

47 Zaslavsky AM, Ayanian JZ, Zaborski LB. The Validity of Race and Ethnicity in Enrollment Data for Medicare Beneficiaries. *Health Services Research*. In press.

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APPENDICES

Chapter 1 Appendices

Appendix 1 Table 1. List of Medicines by ATC

Therapeutic Area	Classification for Analysis	Molecule Name	ATC2 Classification	ATC4 Classification
DIABETES				
	Antidiabetics	ACARBOSE	A10 (DRUGS USED IN DIABETES)	A10L0 (A-GLUCOSIDASE INH A-DIAB)
	Antidiabetics	BUFORMIN	A10 (DRUGS USED IN DIABETES)	A10J1 (BIGUANIDE A-DIABS PLAIN)
	Antidiabetics	CHLORPROPAMIDE	A10 (DRUGS USED IN DIABETES)	A10H0 (SULPHONYLUREA A-DIABS)
	Antidiabetics	EXENATIDE	A10 (DRUGS USED IN DIABETES)	A10S0 (GLP-1 AGONIST A-DIABS)
	Antidiabetics	GLIBENCLAMIDE	A10 (DRUGS USED IN DIABETES)	A10H0 (SULPHONYLUREA A-DIABS)
	Antidiabetics	GLIBENCLAMIDE#METFORMIN	A10 (DRUGS USED IN DIABETES)	A10J2 (BIGUANIDE & S-UREA COMBS)
	Antidiabetics	GLICLAZIDE	A10 (DRUGS USED IN DIABETES)	A10H0 (SULPHONYLUREA A-DIABS)
	Antidiabetics	GLICLAZIDE#METFORMIN	A10 (DRUGS USED IN DIABETES)	A10J2 (BIGUANIDE & S-UREA COMBS)
	Antidiabetics	GLIMEPIRIDE	A10 (DRUGS USED IN DIABETES)	A10H0 (SULPHONYLUREA A-DIABS)
	Antidiabetics	GLIMEPIRIDE#METFORMIN	A10 (DRUGS USED IN DIABETES)	A10J2 (BIGUANIDE & S-UREA COMBS)
	Antidiabetics	GLIMEPIRIDE#ROSIGLITAZONE	A10 (DRUGS USED IN DIABETES)	A10K2 (GLITAZONE & S-UREA COMBS)
	Antidiabetics	GLIPIZIDE	A10 (DRUGS USED IN DIABETES)	A10H0 (SULPHONYLUREA A-DIABS)
	Antidiabetics	GLIQUIDONE	A10 (DRUGS USED IN DIABETES)	A10H0 (SULPHONYLUREA A-DIABS)
	Antidiabetics	METFORMIN	A10 (DRUGS USED IN DIABETES)	A10J1 (BIGUANIDE A-DIABS PLAIN)
	Antidiabetics	METFORMIN#PIOGLITAZONE	A10 (DRUGS USED IN DIABETES)	A10K3 (GLITAZONE & BIGUAN COMBS)
	Antidiabetics	METFORMIN#ROSIGLITAZONE	A10 (DRUGS USED IN DIABETES)	A10K3 (GLITAZONE & BIGUAN COMBS)
	Antidiabetics	METFORMIN#SITAGLIPTIN	A10 (DRUGS USED IN DIABETES)	A10N3 (DPP-IV INH & BIGUAN COMB)
	Antidiabetics	METFORMIN#VILDAGLIPTIN	A10 (DRUGS USED IN DIABETES)	A10N3 (DPP-IV INH & BIGUAN COMB)
	Antidiabetics	PIOGLITAZONE	A10 (DRUGS USED IN DIABETES)	A10K1 (GLITAZONE A-DIABS PLAIN)
	Antidiabetics	REPAGLINIDE	A10 (DRUGS USED IN DIABETES)	A10M1 (GLINIDE A-DIABS PLAIN)
	Antidiabetics	ROSIGLITAZONE	A10 (DRUGS USED IN DIABETES)	A10K1 (GLITAZONE A-DIABS PLAIN)
	Antidiabetics	SITAGLIPTIN	A10 (DRUGS USED IN DIABETES)	A10N1 (DPP-IV INH A-DIAB PLAIN)
	Antidiabetics	VILDAGLIPTIN	A10 (DRUGS USED IN DIABETES)	A10N1 (DPP-IV INH A-DIAB PLAIN)
	Antidiabetics	VOGLIBOSE	A10 (DRUGS USED IN DIABETES)	A10L0 (A-GLUCOSIDASE INH A-DIAB)
	Insulins	INSULIN ASPART	A10 (DRUGS USED IN DIABETES)	A10C1 (H INSUL+ANG FAST ACT)
	Insulins	INSULIN ASPART#INSULIN ASPART PROTAMINE CRYSTALLINE	A10 (DRUGS USED IN DIABETES)	A10C3 (H INSUL+ANG INT+FAST ACT)
	Insulins	INSULIN DETEMIR	A10 (DRUGS USED IN DIABETES)	A10C5 (H INSUL+ANG LONG ACT)
	Insulins	INSULIN GLARGINE	A10 (DRUGS USED IN DIABETES)	A10C5 (H INSUL+ANG LONG ACT)
	Insulins	INSULIN HUMAN BASE	A10 (DRUGS USED IN DIABETES)	A10C1 (H INSUL+ANG FAST ACT)
	Insulins	INSULIN HUMAN BASE#INSULIN HUMAN ISOPHANE	A10 (DRUGS USED IN DIABETES)	A10C3 (H INSUL+ANG INT+FAST ACT)
	Insulins	INSULIN HUMAN ISOPHANE	A10 (DRUGS USED IN DIABETES)	A10C2 (H INSUL+ANG INTERMED ACT)
	Insulins	INSULIN HUMAN ZINC SUSPENSION (COMPOUND)	A10 (DRUGS USED IN DIABETES)	A10C4 (H INSUL+ANG INT+LONG ACT)
	Insulins	INSULIN HUMAN ZINC SUSPENSION (CRYSTALLINE)	A10 (DRUGS USED IN DIABETES)	A10C5 (H INSUL+ANG LONG ACT)
	Insulins	INSULIN LISPRO	A10 (DRUGS USED IN DIABETES)	A10C1 (H INSUL+ANG FAST ACT)
	Insulins	INSULIN LISPRO#INSULIN LISPRO PROTAMINE	A10 (DRUGS USED IN DIABETES)	A10C1 (H INSUL+ANG FAST ACT)
	Insulins	INSULIN PORCINE BASE	A10 (DRUGS USED IN DIABETES)	A10D0 (ANIMAL INSULINS)
	Insulins	INSULIN PORCINE ISOPHANE	A10 (DRUGS USED IN DIABETES)	A10D0 (ANIMAL INSULINS)
	Insulins	INSULIN PORCINE ZINC SUSPENSION (COMPOUND)	A10 (DRUGS USED IN DIABETES)	A10D0 (ANIMAL INSULINS)

Appendix 1 Table 1. List of Medicines by ATC (continued)

Therapeutic Area	Classification for Analysis	Molecule Name	ATC2 Classification	ATC4 Classification
CARIOVASCULAR DISEASE				
	Antihypertensives	AJMALICINE#BUTIZIDE#RESCINNAMINE#RESERPINE	C2 (ANTIHYPERTENSIVES)	C2D0 (RAUWOLF ALK+OTH COM+DIUR)
	Antihypertensives	BUNAZOSIN	C2 (ANTIHYPERTENSIVES)	C2A2 (ANTIHYPER.PL MAINLY PERI)
	Antihypertensives	CLONIDINE	C2 (ANTIHYPERTENSIVES)	C2A1 (ANTIHYPER.PL MAINLY CENT)
	Antihypertensives	CLOPAMIDE#DIHYDROERGOCRISTINE#RESERPINE	C2 (ANTIHYPERTENSIVES)	C2D0 (RAUWOLF ALK+OTH COM+DIUR)
	Antihypertensives	CLOPAMIDE#RESERPINE	C2 (ANTIHYPERTENSIVES)	C2D0 (RAUWOLF ALK+OTH COM+DIUR)
	Antihypertensives	DIHYDRALAZINE	C2 (ANTIHYPERTENSIVES)	C2A2 (ANTIHYPER.PL MAINLY PERI)
	Antihypertensives	DOXAZOSIN	C2 (ANTIHYPERTENSIVES)	C2A2 (ANTIHYPER.PL MAINLY PERI)
	Antihypertensives	HYDRALAZINE	C2 (ANTIHYPERTENSIVES)	C2A2 (ANTIHYPER.PL MAINLY PERI)
	Antihypertensives	HYDRALAZINE#HYDROCHLOROTHIAZIDE#RESERPINE	C2 (ANTIHYPERTENSIVES)	C2B2 (A-HYPERT(N V)MAINLY PERI)
	Antihypertensives	KETANSERIN	C2 (ANTIHYPERTENSIVES)	C2A2 (ANTIHYPER.PL MAINLY PERI)
	Antihypertensives	METHYLDOPA	C2 (ANTIHYPERTENSIVES)	C2A1 (ANTIHYPER.PL MAINLY CENT)
	Antihypertensives	MINOXIDIL	C2 (ANTIHYPERTENSIVES)	C2A2 (ANTIHYPER.PL MAINLY PERI)
	Antihypertensives	NITROPRUSSIDE	C2 (ANTIHYPERTENSIVES)	C2A2 (ANTIHYPER.PL MAINLY PERI)
	Antihypertensives	PRAZOSIN	C2 (ANTIHYPERTENSIVES)	C2A2 (ANTIHYPER.PL MAINLY PERI)
	Antihypertensives	RESERPINE	C2 (ANTIHYPERTENSIVES)	C2C0 (RAUWLF ALK+OTH A-HY HERB)
	Antihypertensives	RILMENIDINE	C2 (ANTIHYPERTENSIVES)	C2A1 (ANTIHYPER.PL MAINLY CENT)
	Antihypertensives	1-PROPANOL	C7 (BETA BLOCKING AGENTS)	C7A0 (B-BLOCKING AGENTS,PLAIN)
	Antihypertensives	AMILORIDE#HYDROCHLOROTHIAZIDE#TIMOLOL	C7 (BETA BLOCKING AGENTS)	C7B1 (B-BLOCK COMB HYPOT/DIURT)
	Antihypertensives	ATENOLOL	C7 (BETA BLOCKING AGENTS)	C7A0 (B-BLOCKING AGENTS,PLAIN)
	Antihypertensives	ATENOLOL#CHLORTALIDONE	C7 (BETA BLOCKING AGENTS)	C7B1 (B-BLOCK COMB HYPOT/DIURT)
	Antihypertensives	BETAXOLOL	C7 (BETA BLOCKING AGENTS)	C7A0 (B-BLOCKING AGENTS,PLAIN)
	Antihypertensives	BISOPROLOL	C7 (BETA BLOCKING AGENTS)	C7A0 (B-BLOCKING AGENTS,PLAIN)
	Antihypertensives	BISOPROLOL#HYDROCHLOROTHIAZIDE	C7 (BETA BLOCKING AGENTS)	C7B1 (B-BLOCK COMB HYPOT/DIURT)
	Antihypertensives	CARVEDILOL	C7 (BETA BLOCKING AGENTS)	C7A0 (B-BLOCKING AGENTS,PLAIN)
	Antihypertensives	CLOPAMIDE#PINDOLOL	C7 (BETA BLOCKING AGENTS)	C7B1 (B-BLOCK COMB HYPOT/DIURT)
	Antihypertensives	LABETALOL	C7 (BETA BLOCKING AGENTS)	C7A0 (B-BLOCKING AGENTS,PLAIN)
	Antihypertensives	METOPROLOL	C7 (BETA BLOCKING AGENTS)	C7A0 (B-BLOCKING AGENTS,PLAIN)
	Antihypertensives	NEBIVOLOL	C7 (BETA BLOCKING AGENTS)	C7A0 (B-BLOCKING AGENTS,PLAIN)
	Antihypertensives	OXPRENOLOL	C7 (BETA BLOCKING AGENTS)	C7A0 (B-BLOCKING AGENTS,PLAIN)
	Antihypertensives	PINDOLOL	C7 (BETA BLOCKING AGENTS)	C7A0 (B-BLOCKING AGENTS,PLAIN)
	Antihypertensives	PROPRANOLOL	C7 (BETA BLOCKING AGENTS)	C7A0 (B-BLOCKING AGENTS,PLAIN)
	Antihypertensives	SOTALOL	C7 (BETA BLOCKING AGENTS	C7A0 (B-BLOCKING AGENTS,PLAIN)
	Antihypertensives	AMLODIPINE	C8 (CALCIUM ANTAGONISTS)	C8A0 (CALCIUM ANTAGONIST PLAIN)
	Antihypertensives	ATENOLOL#NIFEDIPINE	C8 (CALCIUM ANTAGONISTS)	C8B2 (CALC ANTAG/B BLOCKR COMB)
	Antihypertensives	BARNIDIPINE	C8 (CALCIUM ANTAGONISTS)	C8A0 (CALCIUM ANTAGONIST PLAIN)
	Antihypertensives	DILTIAZEM	C8 (CALCIUM ANTAGONISTS)	C8A0 (CALCIUM ANTAGONIST PLAIN)
	Antihypertensives	FELODIPINE	C8 (CALCIUM ANTAGONISTS)	C8A0 (CALCIUM ANTAGONIST PLAIN)

Appendix 1 Table 1. List of Medicines by ATC (continued)

Therapeutic Area	Classification for Analysis	Molecule Name	ATC2 Classification	ATC4 Classification
	Antihypertensives	GALLOPAMIL	C8 (CALCIUM ANTAGONISTS)	C8A0 (CALCIUM ANTAGONIST PLAIN)
	Antihypertensives	ISRADIPINE	C8 (CALCIUM ANTAGONISTS)	C8A0 (CALCIUM ANTAGONIST PLAIN)
	Antihypertensives	LACIDIPINE	C8 (CALCIUM ANTAGONISTS)	C8A0 (CALCIUM ANTAGONIST PLAIN)
	Antihypertensives	LERCANIDIPINE	C8 (CALCIUM ANTAGONISTS)	C8A0 (CALCIUM ANTAGONIST PLAIN)
	Antihypertensives	MANIDIPINE	C8 (CALCIUM ANTAGONISTS)	C8A0 (CALCIUM ANTAGONIST PLAIN)
	Antihypertensives	MIBEFRADIL	C8 (CALCIUM ANTAGONISTS)	C8A0 (CALCIUM ANTAGONIST PLAIN)
	Antihypertensives	NICARDIPINE	C8 (CALCIUM ANTAGONISTS)	C8A0 (CALCIUM ANTAGONIST PLAIN)
	Antihypertensives	NIFEDIPINE	C8 (CALCIUM ANTAGONISTS)	C8A0 (CALCIUM ANTAGONIST PLAIN)
	Antihypertensives	NISOLDIPINE	C8 (CALCIUM ANTAGONISTS)	C8A0 (CALCIUM ANTAGONIST PLAIN)
	Antihypertensives	NITRENDIPINE	C8 (CALCIUM ANTAGONISTS)	C8A0 (CALCIUM ANTAGONIST PLAIN)
	Antihypertensives	VERAPAMIL	C8 (CALCIUM ANTAGONISTS)	C8A0 (CALCIUM ANTAGONIST PLAIN)
	Antihypertensives	AMILORIDE	C3 (DIURETICS)	C3A1 (POT SPARING AGENTS PLAIN)
	Antihypertensives	AMILORIDE#HYDROCHLOROTHIAZIDE	C3 (DIURETICS)	C3A5 (POT SPARING+THIAZ COMBS)
	Antihypertensives	BAROSMA BETULINA#CAPSICUM#METHYLENE BLUE#URGINEA SCI	C3 (DIURETICS)	C3A6 (OTHER DIURETICS)
	Antihypertensives	BAROSMA BETULINA#HYOSCYAMUS ALBUS#POTASSIUM	C3 (DIURETICS)	C3A6 (OTHER DIURETICS)
	Antihypertensives	BENDROFLUMETHIAZIDE#POTASSIUM	C3 (DIURETICS)	C3A3 (THIAZIDE+ANALOGUE PLAIN)
	Antihypertensives	BUMETANIDE	C3 (DIURETICS)	C3A2 (LOOP DIURETICS PLAIN)
	Antihypertensives	FUROSEMIDE	C3 (DIURETICS)	C3A2 (LOOP DIURETICS PLAIN)
	Antihypertensives	HYDROCHLOROTHIAZIDE	C3 (DIURETICS)	C3A3 (THIAZIDE+ANALOGUE PLAIN)
	Antihypertensives	HYDROCHLOROTHIAZIDE#TRIAMTERENE	C3 (DIURETICS)	C3A5 (POT SPARING+THIAZ COMBS)
	Antihypertensives	INDAPAMIDE	C3 (DIURETICS)	C3A3 (THIAZIDE+ANALOGUE PLAIN)
	Antihypertensives	SPIRONOLACTONE	C3 (DIURETICS)	C3A1 (POT SPARING AGENTS PLAIN)
	Antihypertensives	TORASEMIDE	C3 (DIURETICS)	C3A2 (LOOP DIURETICS PLAIN)
	Antihypertensives	TRIPAMIDE	C3 (DIURETICS)	C3A3 (THIAZIDE+ANALOGUE PLAIN)
	Antihypertensives	XIPAMIDE	C3 (DIURETICS)	C3A3 (THIAZIDE+ANALOGUE PLAIN)
	Antihypertensives	ALISKIREN	C9 (RENIN-ANGIOTEN SYS AGENT)	C9X0 (OTH RENIN-ANGIOTEN AGENT)
	Antihypertensives	ALISKIREN#HYDROCHLOROTHIAZIDE	C9 (RENIN-ANGIOTEN SYS AGENT)	C9X0 (OTH RENIN-ANGIOTEN AGENT)
	Antihypertensives	AMLODIPINE#VALSARTAN	C9 (RENIN-ANGIOTEN SYS AGENT)	C9D3 (AT2 ANTG COMB CALC ANTAG)
	Antihypertensives	CANDESARTAN CILEXETIL	C9 (RENIN-ANGIOTEN SYS AGENT)	C9C0 (ANGIOTEN-II ANTAG, PLAIN)
	Antihypertensives	CANDESARTAN CILEXETIL#HYDROCHLOROTHIAZIDE	C9 (RENIN-ANGIOTEN SYS AGENT)	C9D1 (AT2 ANTG COMB C2 &/O DIU)
	Antihypertensives	CAPTOPRIL	C9 (RENIN-ANGIOTEN SYS AGENT)	C9A0 (ACE INHIBITORS PLAIN)
	Antihypertensives	CILAZAPRIL	C9 (RENIN-ANGIOTEN SYS AGENT)	C9A0 (ACE INHIBITORS PLAIN)
	Antihypertensives	DELAPRIL	C9 (RENIN-ANGIOTEN SYS AGENT)	C9A0 (ACE INHIBITORS PLAIN)
	Antihypertensives	ENALAPRIL	C9 (RENIN-ANGIOTEN SYS AGENT)	C9A0 (ACE INHIBITORS PLAIN)
	Antihypertensives	EPROSARTAN	C9 (RENIN-ANGIOTEN SYS AGENT)	C9C0 (ANGIOTEN-II ANTAG, PLAIN)
	Antihypertensives	FOSINOPRIL	C9 (RENIN-ANGIOTEN SYS AGENT)	C9A0 (ACE INHIBITORS PLAIN)
	Antihypertensives	FOSINOPRIL#HYDROCHLOROTHIAZIDE	C9 (RENIN-ANGIOTEN SYS AGENT)	C9B1 (ACE INH COMB+A-HYP/DIUR)
	Antihypertensives	HYDROCHLOROTHIAZIDE#IRBESARTAN	C9 (RENIN-ANGIOTEN SYS AGENT)	C9D1 (AT2 ANTG COMB C2 &/O DIU)

Appendix 1 Table 1. List of Medicines by ATC (continued)

Therapeutic Area	Classification for Analysis	Molecule Name	ATC2 Classification	ATC4 Classification
	Antihypertensives	HYDROCHLOROTHIAZIDE#LOSARTAN	C9 (RENIN-ANGIOTEN SYS AGENT)	C9D1 (AT2 ANTG COMB C2 &/O DIU)
	Antihypertensives	HYDROCHLOROTHIAZIDE#OLMESARTAN MEDOXOMIL	C9 (RENIN-ANGIOTEN SYS AGENT)	C9D1 (AT2 ANTG COMB C2 &/O DIU)
	Antihypertensives	HYDROCHLOROTHIAZIDE#QUINAPRIL	C9 (RENIN-ANGIOTEN SYS AGENT)	C9B1 (ACE INH COMB+A-HYP/DIUR)
	Antihypertensives	HYDROCHLOROTHIAZIDE#RAMIPRIL	C9 (RENIN-ANGIOTEN SYS AGENT)	C9B1 (ACE INH COMB+A-HYP/DIUR)
	Antihypertensives	HYDROCHLOROTHIAZIDE#TELMISARTAN	C9 (RENIN-ANGIOTEN SYS AGENT)	C9D1 (AT2 ANTG COMB C2 &/O DIU)
	Antihypertensives	HYDROCHLOROTHIAZIDE#VALSARTAN	C9 (RENIN-ANGIOTEN SYS AGENT)	C9D1 (AT2 ANTG COMB C2 &/O DIU)
	Antihypertensives	IMIDAPRIL	C9 (RENIN-ANGIOTEN SYS AGENT)	C9A0 (ACE INHIBITORS PLAIN)
	Antihypertensives	INDAPAMIDE#PERINDOPRIL	C9 (RENIN-ANGIOTEN SYS AGENT)	C9B1 (ACE INH COMB+A-HYP/DIUR)
	Antihypertensives	IRBESARTAN	C9 (RENIN-ANGIOTEN SYS AGENT)	C9C0 (ANGIOTEN-II ANTAG, PLAIN)
	Antihypertensives	LISINOPRIL	C9 (RENIN-ANGIOTEN SYS AGENT)	C9A0 (ACE INHIBITORS PLAIN)
	Antihypertensives	LOSARTAN	C9 (RENIN-ANGIOTEN SYS AGENT)	C9C0 (ANGIOTEN-II ANTAG, PLAIN)
	Antihypertensives	OLMESARTAN MEDOXOMIL	C9 (RENIN-ANGIOTEN SYS AGENT)	C9C0 (ANGIOTEN-II ANTAG, PLAIN)
	Antihypertensives	PERINDOPRIL	C9 (RENIN-ANGIOTEN SYS AGENT)	C9A0 (ACE INHIBITORS PLAIN)
	Antihypertensives	QUINAPRIL	C9 (RENIN-ANGIOTEN SYS AGENT)	C9A0 (ACE INHIBITORS PLAIN)
	Antihypertensives	RAMIPRIL	C9 (RENIN-ANGIOTEN SYS AGENT)	C9A0 (ACE INHIBITORS PLAIN)
	Antihypertensives	TELMISARTAN	C9 (RENIN-ANGIOTEN SYS AGENT)	C9C0 (ANGIOTEN-II ANTAG, PLAIN)
	Antihypertensives	VALSARTAN	C9 (RENIN-ANGIOTEN SYS AGENT)	C9C0 (ANGIOTEN-II ANTAG, PLAIN)
	Cardiac Therapy	ADENOSINE	C1 (CARDIAC THERAPY)	C1B0 (ANTIARRHYTHMICS)
	Cardiac Therapy	AMIODARONE	C1 (CARDIAC THERAPY)	C1B0 (ANTIARRHYTHMICS)
	Cardiac Therapy	AMRINONE	C1 (CARDIAC THERAPY)	C1F0 (POSITIVE INOTROPIC AGENT)
	Cardiac Therapy	CAFFEINE#ETAMIVAN	C1 (CARDIAC THERAPY)	C1C1 (CARDIAC STM EX DOPAM AGT)
	Cardiac Therapy	DIGITALIS PURPUREA	C1 (CARDIAC THERAPY)	C1A1 (CARDIAC GLYCOSIDES PLAIN)
	Cardiac Therapy	DIGITOXIN	C1 (CARDIAC THERAPY)	C1A1 (CARDIAC GLYCOSIDES PLAIN)
	Cardiac Therapy	DIGOXIN	C1 (CARDIAC THERAPY)	C1A1 (CARDIAC GLYCOSIDES PLAIN)
	Cardiac Therapy	DISOPYRAMIDE	C1 (CARDIAC THERAPY)	C1B0 (ANTIARRHYTHMICS)
	Cardiac Therapy	DOBUTAMINE	C1 (CARDIAC THERAPY)	C1C2 (CARDIAC DOPAMINERG AGENT)
	Cardiac Therapy	DOPAMINE	C1 (CARDIAC THERAPY)	C1C2 (CARDIAC DOPAMINERG AGENT)
	Cardiac Therapy	EPINEPHRINE	C1 (CARDIAC THERAPY)	C1C1 (CARDIAC STM EX DOPAM AGT)
	Cardiac Therapy	ETAFEDRINE	C1 (CARDIAC THERAPY)	C1C1 (CARDIAC STM EX DOPAM AGT)
	Cardiac Therapy	ETILEFRINE	C1 (CARDIAC THERAPY)	C1C1 (CARDIAC STM EX DOPAM AGT)
	Cardiac Therapy	FLECAINIDE	C1 (CARDIAC THERAPY)	C1B0 (ANTIARRHYTHMICS)
	Cardiac Therapy	GLYCINE MAX#UBIDECARENONE	C1 (CARDIAC THERAPY)	C1X0 (ALL OTHER CARDIAC PREPS)
	Cardiac Therapy	ISOPRENALINE	C1 (CARDIAC THERAPY)	C1C1 (CARDIAC STM EX DOPAM AGT)
	Cardiac Therapy	ISOSORBIDE DINITRATE	C1 (CARDIAC THERAPY)	C1E0 (NITRITES AND NITRATES)
	Cardiac Therapy	ISOSORBIDE MONONITRATE	C1 (CARDIAC THERAPY)	C1E0 (NITRITES AND NITRATES)
	Cardiac Therapy	IVABRADINE	C1 (CARDIAC THERAPY)	C1D0 (CORONRY THER EXC C AN+NI)
	Cardiac Therapy	LIDOCAINE	C1 (CARDIAC THERAPY)	C1B0 (ANTIARRHYTHMICS)
	Cardiac Therapy	MAGNESIUM#POTASSIUM#PROCAINE	C1 (CARDIAC THERAPY)	C1X0 (ALL OTHER CARDIAC PREPS)

Appendix 1 Table 1. List of Medicines by ATC (continued)

Therapeutic Area	Classification for Analysis	Molecule Name	ATC2 Classification	ATC4 Classification
	Cardiac Therapy	METARAMINOL	C1 (CARDIAC THERAPY)	C1C1 (CARDIAC STM EX DOPAM AGT)
	Cardiac Therapy	METILDIGOXIN	C1 (CARDIAC THERAPY)	C1A1 (CARDIAC GLYCOSIDES PLAIN)
	Cardiac Therapy	MEXILETINE	C1 (CARDIAC THERAPY)	C1B0 (ANTIARRHYTHMICS)
	Cardiac Therapy	MIDODRINE	C1 (CARDIAC THERAPY)	C1C1 (CARDIAC STM EX DOPAM AGT)
	Cardiac Therapy	MILRINONE	C1 (CARDIAC THERAPY)	C1F0 (POSITIVE INOTROPIC AGENT)
	Cardiac Therapy	NITROGLYCERIN	C1 (CARDIAC THERAPY)	C1E0 (NITRITES AND NITRATES)
	Cardiac Therapy	NOREPINEPHRINE	C1 (CARDIAC THERAPY)	C1C1 (CARDIAC STM EX DOPAM AGT)
	Cardiac Therapy	OXYFEDRINE	C1 (CARDIAC THERAPY)	C1D0 (CORONRY THER EXC CAN+NI)
	Cardiac Therapy	PENTAERYTHRITYL TETRANITRATE	C1 (CARDIAC THERAPY)	C1E0 (NITRITES AND NITRATES)
	Cardiac Therapy	PROCAINAMIDE	C1 (CARDIAC THERAPY)	C1B0 (ANTIARRHYTHMICS)
	Cardiac Therapy	PROPAFENONE	C1 (CARDIAC THERAPY)	C1B0 (ANTIARRHYTHMICS)
	Cardiac Therapy	QUINIDINE	C1 (CARDIAC THERAPY)	C1B0 (ANTIARRHYTHMICS)
	Cardiac Therapy	TOCAINIDE	C1 (CARDIAC THERAPY)	C1B0 (ANTIARRHYTHMICS)
	Cardiac Therapy	TRIMETAZIDINE	C1 (CARDIAC THERAPY)	C1D0 (CORONRY THER EXC CAN+NI)
	Cardiac Therapy	UBIDECARENONE	C1 (CARDIAC THERAPY)	C1X0 (ALL OTHER CARDIAC PREPS)
	Cardiac Therapy	UBIQUINONE(S)	C1 (CARDIAC THERAPY)	C1X0 (ALL OTHER CARDIAC PREPS)
	Lipid Regulating	ACIPIMOX	C10 (LIP.REG./ANTI-ATH. PREPS)	C10A9 (OTH.CHOLEST&TRIGLY.REGUL)
	Lipid Regulating	ALLIUM SATIVUM	C10 (LIP.REG./ANTI-ATH. PREPS)	C10B0 (ANTI-ATHEROMA NATRL ORIG)
	Lipid Regulating	ALLIUM SATIVUM#ARACHIS HYPOGAEA	C10 (LIP.REG./ANTI-ATH. PREPS)	C10B0 (ANTI-ATHEROMA NATRL ORIG)
	Lipid Regulating	ALLIUM SATIVUM#SOYA LECITHIN	C10 (LIP.REG./ANTI-ATH. PREPS)	C10B0 (ANTI-ATHEROMA NATRL ORIG)
	Lipid Regulating	AMLODIPINE#ATORVASTATIN	C11 (C.V. MULTITH. COMB PROD)	C11A1 (LIPREG.CV.MULT-TH.FX.COM)
	Lipid Regulating	ATORVASTATIN	C10 (LIP.REG./ANTI-ATH. PREPS)	C10A1 (STATINS (HMG-COA RED))
	Lipid Regulating	BEZAFIBRATE	C10 (LIP.REG./ANTI-ATH. PREPS)	C10A2 (FIBRATES)
	Lipid Regulating	CERIVASTATIN	C10 (LIP.REG./ANTI-ATH. PREPS)	C10A1 (STATINS (HMG-COA RED))
	Lipid Regulating	COLESTYRAMINE	C10 (LIP.REG./ANTI-ATH. PREPS)	C10A3 (ION-EXCHANGE RESINS)
	Lipid Regulating	DOCOSAHEXANOIC ACID#EICOSAPENTAENOIC ACID	C10 (LIP.REG./ANTI-ATH. PREPS)	C10B0 (ANTI-ATHEROMA NATRL ORIG)
	Lipid Regulating	DOCOSAHEXANOIC ACID#EICOSAPENTAENOIC ACID#VITAMIN E	C10 (LIP.REG./ANTI-ATH. PREPS)	C10B0 (ANTI-ATHEROMA NATRL ORIG)
	Lipid Regulating	EZETIMIBE	C10 (LIP.REG./ANTI-ATH. PREPS)	C10A9 (OTH.CHOLEST&TRIGLY.REGUL)
	Lipid Regulating	EZETIMIBE#SIMVASTATIN	C10 (LIP.REG./ANTI-ATH. PREPS)	C10C0 (LIP.REG.CO.W.OTH.LIP.REG)
	Lipid Regulating	FENOFIBRATE	C10 (LIP.REG./ANTI-ATH. PREPS)	C10A2 (FIBRATES)
	Lipid Regulating	FISH	C10 (LIP.REG./ANTI-ATH. PREPS)	C10B0 (ANTI-ATHEROMA NATRL ORIG)
	Lipid Regulating	FISH#SOYA LECITHIN	C10 (LIP.REG./ANTI-ATH. PREPS)	C10B0 (ANTI-ATHEROMA NATRL ORIG)
	Lipid Regulating	FLUVASTATIN	C10 (LIP.REG./ANTI-ATH. PREPS)	C10A1 (STATINS (HMG-COA RED))
	Lipid Regulating	GEMFIBROZIL	C10 (LIP.REG./ANTI-ATH. PREPS)	C10A2 (FIBRATES)
	Lipid Regulating	LECITHIN	C10 (LIP.REG./ANTI-ATH. PREPS)	C10B0 (ANTI-ATHEROMA NATRL ORIG)
	Lipid Regulating	LECITHIN#SOYA LECITHIN	C10 (LIP.REG./ANTI-ATH. PREPS)	C10B0 (ANTI-ATHEROMA NATRL ORIG)
	Lipid Regulating	NICOTINIC ACID	C10 (LIP.REG./ANTI-ATH. PREPS)	C10A9 (OTH.CHOLEST&TRIGLY.REGUL)
	Lipid Regulating	PITAVASTATIN	C10 (LIP.REG./ANTI-ATH. PREPS)	C10A1 (STATINS (HMG-COA RED))

Appendix 1 Table 1. List of Medicines by ATC (continued)

Therapeutic Area	Classification for Analysis	Molecule Name	ATC2 Classification	ATC4 Classification
	Lipid Regulating	PRAVASTATIN	C10 (LIP.REG./ANTI-ATH. PREPS)	C10A1 (STATINS (HMG-COA RED))
	Lipid Regulating	PROBUCOL	C10 (LIP.REG./ANTI-ATH. PREPS)	C10A9 (OTH.CHOLEST&TRIGLY.REGUL)
	Lipid Regulating	PYRICARBATE	C10 (LIP.REG./ANTI-ATH. PREPS)	C10A9 (OTH.CHOLEST&TRIGLY.REGUL)
	Lipid Regulating	ROSUVASTATIN	C10 (LIP.REG./ANTI-ATH. PREPS)	C10A1 (STATINS (HMG-COA RED))
	Lipid Regulating	SALMON	C10 (LIP.REG./ANTI-ATH. PREPS)	C10B0 (ANTI-ATHEROMA NATRL ORIG)
	Lipid Regulating	SIMVASTATIN	C10 (LIP.REG./ANTI-ATH. PREPS)	C10A1 (STATINS (HMG-COA RED))
	Lipid Regulating	SOYA LECITHIN	C10 (LIP.REG./ANTI-ATH. PREPS)	C10B0 (ANTI-ATHEROMA NATRL ORIG)
CANCER				
	Antineoplastics	ALEMTUZUMAB	L1 (ANTINEOPLASTICS)	L1X3 (ANTINEOPLASTIC MABS)
	Antineoplastics	ALTRETAMINE	L1 (ANTINEOPLASTICS)	L1A0 (ALKYLATING AGENTS)
	Antineoplastics	ASPARAGINASE	L1 (ANTINEOPLASTICS)	L1X9 (ALL OTH. ANTINEOPLASTICS)
	Antineoplastics	AZACITIDINE	L1 (ANTINEOPLASTICS)	L1B0 (ANTIMETABOLITES)
	Antineoplastics	BEVACIZUMAB	L1 (ANTINEOPLASTICS)	L1X3 (ANTINEOPLASTIC MABS)
	Antineoplastics	BLEOMYCIN	L1 (ANTINEOPLASTICS)	L1D0 (ANTINEOPLAS. ANTIBIOTICS)
	Antineoplastics	BORTEZOMIB	L1 (ANTINEOPLASTICS)	L1X9 (ALL OTH. ANTINEOPLASTICS)
	Antineoplastics	BUSULFAN	L1 (ANTINEOPLASTICS)	L1A0 (ALKYLATING AGENTS)
	Antineoplastics	CAPECITABINE	L1 (ANTINEOPLASTICS)	L1B0 (ANTIMETABOLITES)
	Antineoplastics	CARBOPLATIN	L1 (ANTINEOPLASTICS)	L1X2 (PLATINUM COMPOUNDS)
	Antineoplastics	CARMUSTINE	L1 (ANTINEOPLASTICS)	L1A0 (ALKYLATING AGENTS)
	Antineoplastics	CETUXIMAB	L1 (ANTINEOPLASTICS)	L1X3 (ANTINEOPLASTIC MABS)
	Antineoplastics	CHLORAMBUCIL	L1 (ANTINEOPLASTICS)	L1A0 (ALKYLATING AGENTS)
	Antineoplastics	CHLORMETHINE	L1 (ANTINEOPLASTICS)	L1A0 (ALKYLATING AGENTS)
	Antineoplastics	CISPLATIN	L1 (ANTINEOPLASTICS)	L1X2 (PLATINUM COMPOUNDS)
	Antineoplastics	CLADRIBINE	L1 (ANTINEOPLASTICS)	L1B0 (ANTIMETABOLITES)
	Antineoplastics	CYCLOPHOSPHAMIDE	L1 (ANTINEOPLASTICS)	L1A0 (ALKYLATING AGENTS)
	Antineoplastics	CYTARABINE	L1 (ANTINEOPLASTICS)	L1B0 (ANTIMETABOLITES)
	Antineoplastics	DACARBAZINE	L1 (ANTINEOPLASTICS)	L1A0 (ALKYLATING AGENTS)
	Antineoplastics	DACTINOMYCIN	L1 (ANTINEOPLASTICS)	L1D0 (ANTINEOPLAS. ANTIBIOTICS)
	Antineoplastics	DASATINIB	L1 (ANTINEOPLASTICS)	L1X4 (A-NEO PROTEIN KINASE INH)
	Antineoplastics	DECITABINE	L1 (ANTINEOPLASTICS)	L1B0 (ANTIMETABOLITES)
	Antineoplastics	DOCETAXEL	L1 (ANTINEOPLASTICS)	L1C0 (VINCA ALKALOIDS)
	Antineoplastics	DOXORUBICIN	L1 (ANTINEOPLASTICS)	L1D0 (ANTINEOPLAS. ANTIBIOTICS)
	Antineoplastics	EPIRUBICIN	L1 (ANTINEOPLASTICS)	L1D0 (ANTINEOPLAS. ANTIBIOTICS)
	Antineoplastics	ERLOTINIB	L1 (ANTINEOPLASTICS)	L1X4 (A-NEO PROTEIN KINASE INH)
	Antineoplastics	ETOPOSIDE	L1 (ANTINEOPLASTICS)	L1C0 (VINCA ALKALOIDS)
	Antineoplastics	FLUDARABINE	L1 (ANTINEOPLASTICS)	L1B0 (ANTIMETABOLITES)
	Antineoplastics	FLUOROURACIL	L1 (ANTINEOPLASTICS)	L1B0 (ANTIMETABOLITES)

Appendix 1 Table 1. List of Medicines by ATC (continued)

Therapeutic Area	Classification for Analysis	Molecule Name	ATC2 Classification	ATC4 Classification
	Antineoplastics	GEFITINIB	L1 (ANTINEOPLASTICS)	L1X4 (A-NEO PROTEIN KINASE INH)
	Antineoplastics	GEMCITABINE	L1 (ANTINEOPLASTICS)	L1B0 (ANTIMETABOLITES)
	Antineoplastics	HYDROXYCARBAMIDE	L1 (ANTINEOPLASTICS)	L1X9 (ALL OTH. ANTINEOPLASTICS)
	Antineoplastics	IBRITUMOMAB TIUXETAN	L1 (ANTINEOPLASTICS)	L1X3 (ANTINEOPLASTIC MABS)
	Antineoplastics	IDARUBICIN	L1 (ANTINEOPLASTICS)	L1D0 (ANTINEOPLAS. ANTIBIOTICS)
	Antineoplastics	IFOSFAMIDE	L1 (ANTINEOPLASTICS)	L1A0 (ALKYLATING AGENTS)
	Antineoplastics	IMATINIB	L1 (ANTINEOPLASTICS)	L1X4 (A-NEO PROTEIN KINASE INH)
	Antineoplastics	IRINOTECAN	L1 (ANTINEOPLASTICS)	L1C0 (VINCA ALKALOIDS)
	Antineoplastics	IXABEPILONE	L1 (ANTINEOPLASTICS)	L1X9 (ALL OTH. ANTINEOPLASTICS)
	Antineoplastics	LAPATINIB	L1 (ANTINEOPLASTICS)	L1X4 (A-NEO PROTEIN KINASE INH)
	Antineoplastics	LOMUSTINE	L1 (ANTINEOPLASTICS)	L1A0 (ALKYLATING AGENTS)
	Antineoplastics	MELPHALAN	L1 (ANTINEOPLASTICS)	L1A0 (ALKYLATING AGENTS)
	Antineoplastics	MERCAPTOPURINE	L1 (ANTINEOPLASTICS)	L1B0 (ANTIMETABOLITES)
	Antineoplastics	METHOTREXATE	L1 (ANTINEOPLASTICS)	L1B0 (ANTIMETABOLITES)
	Antineoplastics	MITOMYCIN	L1 (ANTINEOPLASTICS)	L1D0 (ANTINEOPLAS. ANTIBIOTICS)
	Antineoplastics	MITOXANTRONE	L1 (ANTINEOPLASTICS)	L1D0 (ANTINEOPLAS. ANTIBIOTICS)
	Antineoplastics	NILOTINIB	L1 (ANTINEOPLASTICS)	L1X4 (A-NEO PROTEIN KINASE INH)
	Antineoplastics	OXALIPLATIN	L1 (ANTINEOPLASTICS)	L1X2 (PLATINUM COMPOUNDS)
	Antineoplastics	PACLITAXEL	L1 (ANTINEOPLASTICS)	L1C0 (VINCA ALKALOIDS)
	Antineoplastics	PEMETREXED	L1 (ANTINEOPLASTICS)	L1B0 (ANTIMETABOLITES)
	Antineoplastics	PROCARBAZINE	L1 (ANTINEOPLASTICS)	L1X9 (ALL OTH. ANTINEOPLASTICS)
	Antineoplastics	RITUXIMAB	L1 (ANTINEOPLASTICS)	L1X3 (ANTINEOPLASTIC MABS)
	Antineoplastics	SORAFENIB	L1 (ANTINEOPLASTICS)	L1X4 (A-NEO PROTEIN KINASE INH)
	Antineoplastics	SUNITINIB	L1 (ANTINEOPLASTICS)	L1X4 (A-NEO PROTEIN KINASE INH)
	Antineoplastics	TEGAFUR	L1 (ANTINEOPLASTICS)	L1B0 (ANTIMETABOLITES)
	Antineoplastics	TEGAFUR#URACIL	L1 (ANTINEOPLASTICS)	L1B0 (ANTIMETABOLITES)
	Antineoplastics	TEMOZOLOMIDE	L1 (ANTINEOPLASTICS)	L1A0 (ALKYLATING AGENTS)
	Antineoplastics	TIOGUANINE	L1 (ANTINEOPLASTICS)	L1B0 (ANTIMETABOLITES)
	Antineoplastics	TOPOTECAN	L1 (ANTINEOPLASTICS)	L1C0 (VINCA ALKALOIDS)
	Antineoplastics	TRASTUZUMAB	L1 (ANTINEOPLASTICS)	L1X3 (ANTINEOPLASTIC MABS)
	Antineoplastics	TRETINOIN	L1 (ANTINEOPLASTICS)	L1X9 (ALL OTH. ANTINEOPLASTICS)
	Antineoplastics	VINBLASTINE	L1 (ANTINEOPLASTICS)	L1C0 (VINCA ALKALOIDS)
	Antineoplastics	VINCRISTINE	L1 (ANTINEOPLASTICS)	L1C0 (VINCA ALKALOIDS)
	Antineoplastics	VINORELBINE	L1 (ANTINEOPLASTICS)	L1C0 (VINCA ALKALOIDS)
	Cytostatic Hormones	AMINOGLUTETHIMIDE	L2 (CYTOSTATIC HORMONE THER)	L2B3 (CYTOSTAT AROMATASE INHIB)
	Cytostatic Hormones	ANASTROZOLE	L2 (CYTOSTATIC HORMONE THER)	L2B3 (CYTOSTAT AROMATASE INHIB)
	Cytostatic Hormones	BICALUTAMIDE	L2 (CYTOSTATIC HORMONE THER)	L2B2 (CYTO ANTI-ANDROGENS)
	Cytostatic Hormones	BUSERELIN	L2 (CYTOSTATIC HORMONE THER)	L2A3 (CYTO GONAD HORMON ANALOG)

Appendix 1 Table 1. List of Medicines by ATC (continued)

Therapeutic Area	Classification for Analysis	Molecule Name	ATC2 Classification	ATC4 Classification
	Cytostatic Hormones	CYPROTERONE	L2 (CYTOSTATIC HORMONE THER)	L2B2 (CYTO ANTI-ANDROGENS)
	Cytostatic Hormones	EXEMESTANE	L2 (CYTOSTATIC HORMONE THER)	L2B3 (CYTOSTAT AROMATASE INHIB)
	Cytostatic Hormones	FLUTAMIDE	L2 (CYTOSTATIC HORMONE THER)	L2B2 (CYTO ANTI-ANDROGENS)
	Cytostatic Hormones	FORMESTANE	L2 (CYTOSTATIC HORMONE THER)	L2B3 (CYTOSTAT AROMATASE INHIB)
	Cytostatic Hormones	FULVESTRANT	L2 (CYTOSTATIC HORMONE THER)	L2B9 (OTH CYTO HORMON ANTAGIST)
	Cytostatic Hormones	GOSERELIN	L2 (CYTOSTATIC HORMONE THER)	L2A3 (CYTO GONAD HORMON ANALOG)
	Cytostatic Hormones	LETROZOLE	L2 (CYTOSTATIC HORMONE THER)	L2B3 (CYTOSTAT AROMATASE INHIB)
	Cytostatic Hormones	LEUPRORELIN	L2 (CYTOSTATIC HORMONE THER)	L2A3 (CYTO GONAD HORMON ANALOG)
	Cytostatic Hormones	MEDROXYPROGESTERONE	L2 (CYTOSTATIC HORMONE THER)	L2A2 (CYTOSTATIC PROGESTOGENS)
	Cytostatic Hormones	MEGESTROL	L2 (CYTOSTATIC HORMONE THER)	L2A2 (CYTOSTATIC PROGESTOGENS)
	Cytostatic Hormones	TAMOXIFEN	L2 (CYTOSTATIC HORMONE THER)	L2B1 (CYTO ANTI-OESTROGENS)
	Cytostatic Hormones	TOREMIFENE	L2 (CYTOSTATIC HORMONE THER)	L2B1 (CYTO ANTI-OESTROGENS)
	Cytostatic Hormones	TRIPTORELIN	L2 (CYTOSTATIC HORMONE THER)	L2A3 (CYTO GONAD HORMON ANALOG)
	Immunostimulating Agents	FILGRASTIM	L3 (IMMUNOSTIMULATING AGENTS)	L3A1 (COLONY-STIMULATING FACT.)
	Immunostimulating Agents	INTERFERON ALFA	L3 (IMMUNOSTIMULATING AGENTS)	L3B1 (INTERFERONS ALPHA)
	Immunostimulating Agents	INTERFERON ALFA-2A	L3 (IMMUNOSTIMULATING AGENTS)	L3B1 (INTERFERONS ALPHA)
	Immunostimulating Agents	INTERFERON ALFA-2B	L3 (IMMUNOSTIMULATING AGENTS)	L3B1 (INTERFERONS ALPHA)
	Immunostimulating Agents	INTERFERON ALFA-N1	L3 (IMMUNOSTIMULATING AGENTS)	L3B1 (INTERFERONS ALPHA)
	Immunostimulating Agents	INTERFERON BETA-1A	L3 (IMMUNOSTIMULATING AGENTS)	L3B2 (INTERFERONS BETA)
	Immunostimulating Agents	INTERFERON BETA-1B	L3 (IMMUNOSTIMULATING AGENTS)	L3B2 (INTERFERONS BETA)
	Immunostimulating Agents	LENOGRASTIM	L3 (IMMUNOSTIMULATING AGENTS)	L3A1 (COLONY-STIMULATING FACT.)
	Immunostimulating Agents	MOLGRAMOSTIM	L3 (IMMUNOSTIMULATING AGENTS)	L3A1 (COLONY-STIMULATING FACT.)
	Immunostimulating Agents	PEGFILGRASTIM	L3 (IMMUNOSTIMULATING AGENTS)	L3A1 (COLONY-STIMULATING FACT.)
	Immunostimulating Agents	TETRACHLORODECAOXIDE	L3 (IMMUNOSTIMULATING AGENTS)	L3A9 (OTH.IMMUNOSTIM.EX.INTFRN)
	Immunostimulating Agents	THYMALFASIN	L3 (IMMUNOSTIMULATING AGENTS)	L3A9 (OTH.IMMUNOSTIM.EX.INTFRN)

Appendix 1 Table 2. Segmented Regression Coefficients: Total Volume*

	INTERCEPT	TIME	INTERVENTION	TIME AFTER INTERVENTION	TIME AFTER INTERVENTION SQUARED**
	Beta	Beta (Std. Err.)	Beta (Std. Err.)	Beta (Std. Err.)	Beta (Std. Err.)
DIABETES					
Insulins					
Hospital	1.6941	**0.0848 (0.0185)**	**0.5151 (0.2400)**	**0.0961 (0.0432)**	**0.0156 (0.0019)**
Retail	0.3485	**-0.0134 (0.0041)**	0.0902 (0.0445)	**0.0288 (0.0046)**	-
Antidiabetics					
Hospital	1252.37	**71.08 (12.05)**	66.40 (167.31)	12.80 (26.17)	**3.08 (1.24)**
Retail	228.87	**6.67 (3.01)**	-63.98 (32.56)	-1.88 (3.37)	-
CARDIOVASCULAR DISEASE					
Antihypertensives					
Hospital	1394.24	**111.96 (17.14)**	**-390.49 (185.18)**	**71.95 (19.17)**	-
Retail	284.98	**8.12 (2.24)**	-39.71 (24.19)	**5.20 (2.50)**	-
Lipid Regulating Agents					
Hospital	193.47	**17.31 (3.33)**	-37.98 (43.19)	-6.02 (7.78)	**2.77 (0.34)**
Retail	136.25	-2.59 (1.31)	-21.37 (14.18)	**11.72 (1.47)**	-
Cardiac Therapy					
Hospital	434.75	**13.92 (4.11)**	**-94.51 (44.37)**	0.63 (4.59)	-
Retail	98.32	1.63 (1.18)	11.50 (15.31)	**-8.80 (2.76)**	**0.32 (0.12)**
CANCER					
Antineoplastics					
Hospital	21.75	**0.72 (0.16)**	-2.02 (1.78)	0.21 (0.18)	-
Retail	0.26	0.004 (0.02)	0.18 (0.37)	0.05 (0.06)	-0.005 (0.002)
Cytostatic Hormones					
Hospital	16.38	**0.69 (0.15)**	-0.66 (1.60)	**0.44 (0.17)**	-
Retail	0.3538	**-0.03 (0.01)**	**0.53 (0.13)**	-0.03 (0.02)	**0.004 (0.001)**
Immunostimulating Agents					
Hospital	0.45	**0.01 (0.004)**	**-0.18 (0.05)**	-0.02 (0.008)	0.0007 (0.0004)
Retail	0.0000066	-0.0000005 (0.000001)	0.0000003 (0.000007)	0.0000005 (0.0000007)	-

* **Bold** signifies statistically significant coefficient (i.e., $p<0.05$)

**Results from quadratic model (which has squared post-policy trend term) were included if quadratic model fits better than linear model.

Appendix 1 Table 3. Absolute Impact of the Reform on Sales of Medicines by Class (one and five years post-policy)*

Therapeutic Class	One Year Impact (in standard units)			Five Year Impact (in standard units)		
	Predicted	**Observed**	**Absolute Change (95% CI)**	**Predicted**	**Observed**	**Absolute Change (95% CI)**
Antidiabetics	2602.91	2769.79	166.87 (-160.98, 494.73)	3669.13	5090.62	**1421.49 (739.57, 2103.42)**
Insulins	3.30	4.45	**1.15 (0.66, 1.64)**	4.58	12.56	**7.98 (6.94, 9.02)**
Cardiac Therapy Agents	699.28	607.27	-92.01 (-201.38, 17.36)	908.12	825.49	-82.63 (-309.66, 144.40)
Lipid Regulating Agents	522.34	504.58	-17.76 (-106.50, 70.97)	781.97	1629.11	**847.14 (659.98, 1034.30)**
Antihypertensives	3521.47	3418.79	-102.68 (-559.16, 353.80)	5200.86	6177.49	**976.62 (29.03, 1924.22)**
Antineoplastics	35.38	34.21	-1.17 (-5.56, 3.22)	46.14	48.13	1.99 (-7.13, 11.11)
Cytostatic Hormones	29.48	30.58	1.10 (-2.85, 5.05)	39.82	47.52	7.70 (-0.50, 15.89)
Immunostimulating Agents	0.65	0.43	**-0.23 (-0.32, -0.13)**	0.81	0.60	**-0.21 (-0.42, -0.01)**

***bold** signifies that change is statistically significant (i.e., confidence interval does not include the null value of 0)

Appendix 1 Table 4. Segmented Regression Coefficients: Hospital Market Share*

	INTERCEPT	TIME	INTERVENTION	TIME AFTER INTERVENTION	TIME AFTER INTERVENTION SQUARED**
	Beta	Beta (Std. Err.)	Beta (Std. Err.)	Beta (Std. Err.)	Beta (Std. Err.)
Insulins (Hospital)					
Originator Brand	-0.0017	**0.0005 (0.0001)**	-0.0004 (0.0017)	-0.0003 (0.0003)	**0.0001 (0.0000002)**
Branded Generic	0.8934	0.0026 (0.0019)	**0.0697 (0.0200)**	**-0.0048 (0.0021)**	-
Generic	0.1083	-0.0030 (0.0019)	**-0.0624 (0.0200)**	0.0031 (0.0021)	-
Antidiabetics (Hospital)					
Originator Brand	0.1601	**-0.0049 (0.0006)**	-0.0028 (0.0064)	**0.0042 (0.0007)**	-
Branded Generic	0.5178	0.0010 (0.0016)	**-0.1233 (0.0178)**	**-0.0045 (0.0017)**	-
Generic	0.0692	0.0005 (0.0011)	**-0.0345 (0.0116)**	-0.000545 (0.0012)	-
GPO	0.2505	0.0034 (0.0018)	**0.1610 (0.0200)**	0.000992 (0.0019)	-
Antihypertentives (Hospital)					
Originator Brand	0.296	**-0.0066 (0.0008)**	-0.0014 (0.0105)	0.0034 (0.0019)	**0.0002 (0.00008)**
Branded Generic	0.4491	**0.0056 (0.0015)**	-0.0214 (0.0191)	**0.0092 (0.0034)**	**-0.0006 (0.0002)**
Generic	0.041	**0.0033 (0.0012)**	**-0.0567 (0.0130)**	**-0.0030 (0.0013)**	-
GPO	0.211	-0.0020 (0.0024)	0.0525 (0.0259)	-0.0022 (0.0027)	-
Lipid Regulating Agents (Hospital)					
Originator Brand	0.5657	**-0.0092 (0.0008)**	**-0.0776 (0.0116)**	**-0.0061 (0.0116)**	**0.0003 (0.00009)**
Branded Generic	0.427	**0.0096 (0.0008)**	**0.0755 (0.0118)**	**0.0055 (0.0017)**	**-0.0003 (0.00009)**
Generic	0.004897	-0.0003 (0.0002)	0.0015 (0.0025)	0.0002 (0.0003)	-
GPO	-0.000482	0.0001 (0.0003)	0.0023 (0.0028)	-0.0003 (0.0003)	-
Cardiac Therapy (Hospital)					
Originator Brand	0.0847	**-0.0014 (0.0004)**	0.0013 (0.0044)	**0.0014 (0.0004)**	
Branded Generic	0.8032	-0.0023 (0.0026)	**-0.1351 (0.0340)**	-0.0093 (0.0061)	**0.0006 (0.0003)**
Generic	0.005095	**0.0031 (0.0009)**	**-0.0426 (0.0093)**	**-0.0030 (0.0010)**	-
GPO	0.0751	0.0015 (0.0030)	**0.2155 (0.0319)**	-0.0010 (0.0033)	-
Antineoplastics (Hospital)					
Originator Brand	0.1554	0.0015 (0.0009)	0.0110 (0.0103)	-0.0014 (0.0010)	-
Branded Generic	0.5518	-0.0011 (0.0020)	-0.0100 (0.0216)	0.0011 (0.0022)	-
Generic	0.2862	-0.0004 (0.0014)	0.0037 (0.0149)	0.0002 (0.0015)	-
Cytostatic Hormones (Hospital)					
Originator Brand	0.4664	-0.0032 (0.0022)	0.0038 (0.0280)	**-0.0127 (0.0050)**	**0.0007 (0.0002)**
Branded Generic	0.5141	**0.0036 (0.0015)**	**-0.0773 (0.0206)**	**0.0195 (0.0035)**	**-0.0013 (0.0002)**
Generic	0.0144	0.0004 (0.0017)	**0.0600 (0.0224)**	-0.0060 (0.0040)	**0.0005 (0.0002)**
Immunostimulating Agents (Hospital)					
Originator Brand	0.9742	0.0007 (0.0015)	**-0.0636 (0.0162)**	**-0.0113 (0.0017)**	-
Branded Generic	-0.000536	0.0001 (0.0013)	**0.0450 (0.0137)**	**0.0108 (0.0014)**	-
Generic	-0.000986	**0.0002 (0.0001)**	-0.0016 (0.0009)	**-0.0003 (0.00009)**	-

* **Bold** signifies statistically significant coefficient (i.e., $p<0.05$)

**Results from quadratic model (which has squared post-policy trend term) were included if quadratic model fits better than linear model.

Appendix 1 Table 5. Absolute Impact of the Reform on Sales of Licensing Status Market Share by Class (one and five years post-policy)*

Therapeutic Class	One Year Impact (in % market share)			Five Year Impact (in % market share)		
	Predicted	Observed	Relative Change (95% CI)	Predicted	Observed	Relative Change (95% CI)
Antidiabetics						
Original/Licensed	0.0672	0.0813	0.0140 (-0.0016, 0.0297)	-0.0061	0.0712	**0.0773 (0.0448, 0.1098)**
Other	0.5371	0.3960	**-0.1412 (-0.1851, -0.0972)**	0.5524	0.3443	**-0.2080 (-0.2966, -0.1195)**
Unbranded	0.0788	0.0421	**-0.0367 (-0.0652, -0.0082)**	0.0864	0.0415	-0.0449 (-0.1041, 0.0144)
GPO	0.3142	0.4792	**0.1649 (0.1156, 0.2143)**	0.3645	0.5444	**0.1798 (0.0805, 0.2792)**
Insulins						
Originator Brand	0.0079	0.0081	0.0002 (-0.0035, 0.0038)	0.0156	0.0461	**0.0305 (0.0228, 0.0382)**
Branded Generic	0.9419	0.9925	**0.0505 (0.0010, 0.1000)**	0.9802	0.9590	-0.0212 (-0.1240, 0.0815)
Generic	0.0501	0.0000	**-0.0501 (-0.0994, -0.0008)**	0.0042	0.0000	-0.0042 (-0.1065, 0.0982)
Antihypertensives						
Originator Brand	0.1697	0.1850	0.0153 (-0.0063, 0.0368)	0.0700	0.2010	**0.1310 (0.0854, 0.1765)**
Branded Generic	0.5557	0.5619	0.0062 (-0.0330, 0.0454)	0.6398	0.5890	-0.0507 (-0.1333, 0.0319)
Generic	0.1029	0.0341	**-0.0688 (-0.1009, -0.0368)**	0.1519	0.0373	**-0.1145 (-0.1811, -0.0480)**
GPO	0.1725	0.2160	0.0435 (-0.0203, 0.1074)	0.1420	0.1520	0.0100 (-0.1225, 0.1425)
Cardiac Therapy						
Originator Brand	0.0588	0.0656	0.0068 (-0.0041, 0.0176)	0.0384	0.0655	**0.0271 (0.0049, 0.0493)**
Branded Generic	0.7594	0.5961	**-0.1633 (-0.2332, -0.0935)**	0.7594	0.5961	**-0.1633 (-0.2332, -0.0935)**
Generic	0.1116	0.0113	**-0.1002 (-0.1477, -0.0528)**	0.1116	0.0113	**-0.1002 (-0.1477, -0.0528)**
GPO	0.1034	0.3149	**0.2115 (0.1329, 0.2901)**	0.1034	0.3149	**0.2115 (0.1329, 0.2901)**
Lipid Regulators						
Originator Brand	0.3905	0.2942	**-0.0963 (-0.1187, -0.0739)**	0.2522	0.1838	**-0.0684 (-0.1158, -0.0210)**
Branded Generic	0.6086	0.7010	**0.0924 (0.0697, 0.1151)**	0.7519	0.8159	**0.0640 (0.0160, 0.1119)**
Generic	-0.0009	0.0015	0.0024 (-0.0038, 0.0085)	-0.0054	0.0004	0.0058 (-0.0070, 0.0186)
GPO	0.0022	0.0033	0.0011 (-0.0058, 0.0079)	0.0044	0.0008	-0.0035 (-0.0177, 0.0106)
Antineoplastics						
Originator Brand	0.1840	0.1894	0.0054 (-0.0201, 0.0308)	0.2066	0.1908	-0.0158 (-0.0675, 0.0359)
Branded Generic	0.5308	0.5252	-0.0056 (-0.0587, 0.0476)	0.5142	0.5252	0.0110 (-0.0993, 0.1214)
Generic	0.2783	0.2827	0.0044 (-0.0323, 0.0412)	0.2721	0.2793	0.0072 (-0.0690, 0.0835)
Cytostatic Hormones						
Originator Brand	0.4058	0.3704	-0.0353 (-0.0928, 0.0222)	0.3579	0.3803	0.0224 (-0.0988, 0.1437)
Branded Generic	0.5821	0.5626	-0.0195 (-0.0609, 0.0218)	0.6358	0.4764	**-0.1595 (-0.2463, -0.0727)**
Generic	0.0221	0.0653	0.0432 (-0.0029, 0.0893)	0.0282	0.1393	**0.1112 (0.0140, 0.2083)**
Immunostimulating Agents						
Originator Brand	0.9875	0.8787	**-0.1087 (-0.1488, -0.0687)**	0.9979	0.7198	**-0.2781 (-0.3612, -0.1951)**
Branded Generic	0.0018	0.0902	**0.0884 (0.0546, 0.1221)**	0.0037	0.2546	**0.2509 (0.1808, 0.3210)**
Generic	0.0036	0.0007	**-0.0028 (-0.0050, -0.0007)**	0.0071	-0.0003	**-0.0074 (-0.0120, -0.0029)**

***bold** signifies that change is statistically significant (i.e., confidence interval does not include the null value of 0)

Appendix 1 Table 6. Hospital Sector Market Share Regression Results by NLEM*

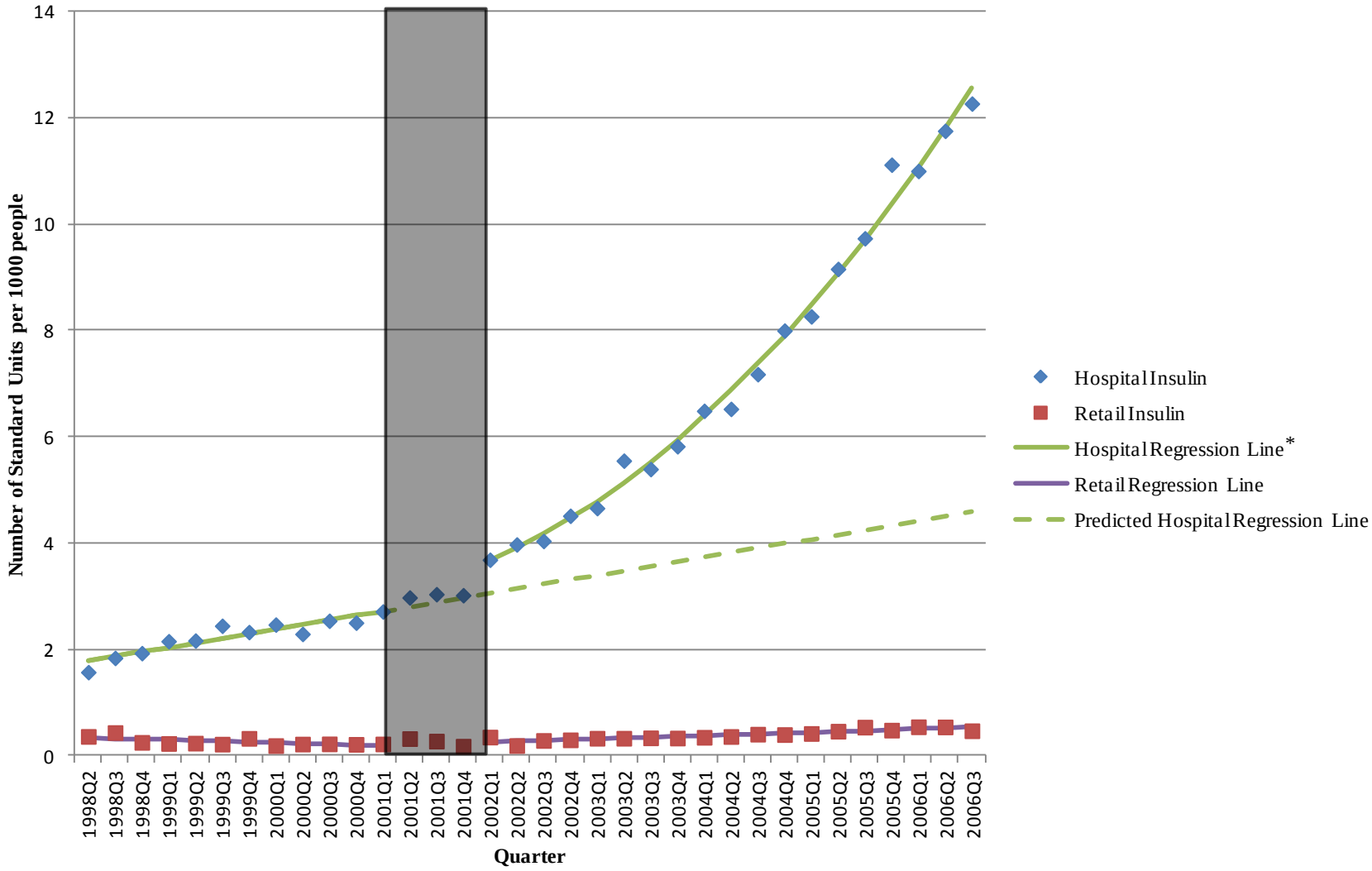
	INTERCEPT	TIME	INTERVENTION	TIME AFTER INTERVENTION	TIME AFTER INTERVENTION SQUARED**	NLEM
	Beta	Beta (Std. Err.)	Beta (Std. Err.)	Beta (Std. Err.)	Beta (Std. Err.)	Beta (Std. Err.)
DIABETES						
Insulins* **	-	-	-	-	-	-
Antidiabetics	0.9995	**-0.0016 (0.0001)**	0.0005 (0.0015)	**0.0014 (0.0002)**	-	**0.0160 (0.0013)**
CARDIOVASCULAR DISEASE						
Antihypertensives	0.9006	**0.0022 (0.0004)**	-0.0010 (0.0057)	**-0.0070 (0.0010)**	**0.0003 (0.0001)**	**-0.0814 (0.0054)**
Lipid Regulating Agents	0.7394	0.0001 (0.0010)	0.0205 (0.0130)	**0.0070 (0.0024)**	-0.0002 (0.0001)	**0.1271 (0.0122)**
Cardiac Therapy	0.8689	**0.0027 (0.0005)**	0.0073 (0.0056)	**-0.0030 (0.0006)**	-	0.0070 (0.0050)
CANCER						
Antineoplastics	0.939	**-0.0076 (0.0008)**	0.0121 (0.0114)	-0.0022 (0.0019)	**0.0003 (0.0001)**	**0.0358 (0.0117)**
Cytostatic Hormones	0.9947	**-0.0019 (0.0004)**	**-0.0099 (0.0043)**	**-0.0021 (0.0005)**	-	**-0.1108 (0.0039)**
Immunostimulating Agents	0.4144	**0.0084 (0.0035)**	**0.0986 (0.0396)**	**0.0100 (0.0047)**	-	-0.0615 (0.0359)

* **Bold** signifies statistically significant coefficient (i.e., $p<0.05$)

**Results from quadratic model (which has squared post-policy trend term) were included if quadratic model fits better than linear model.

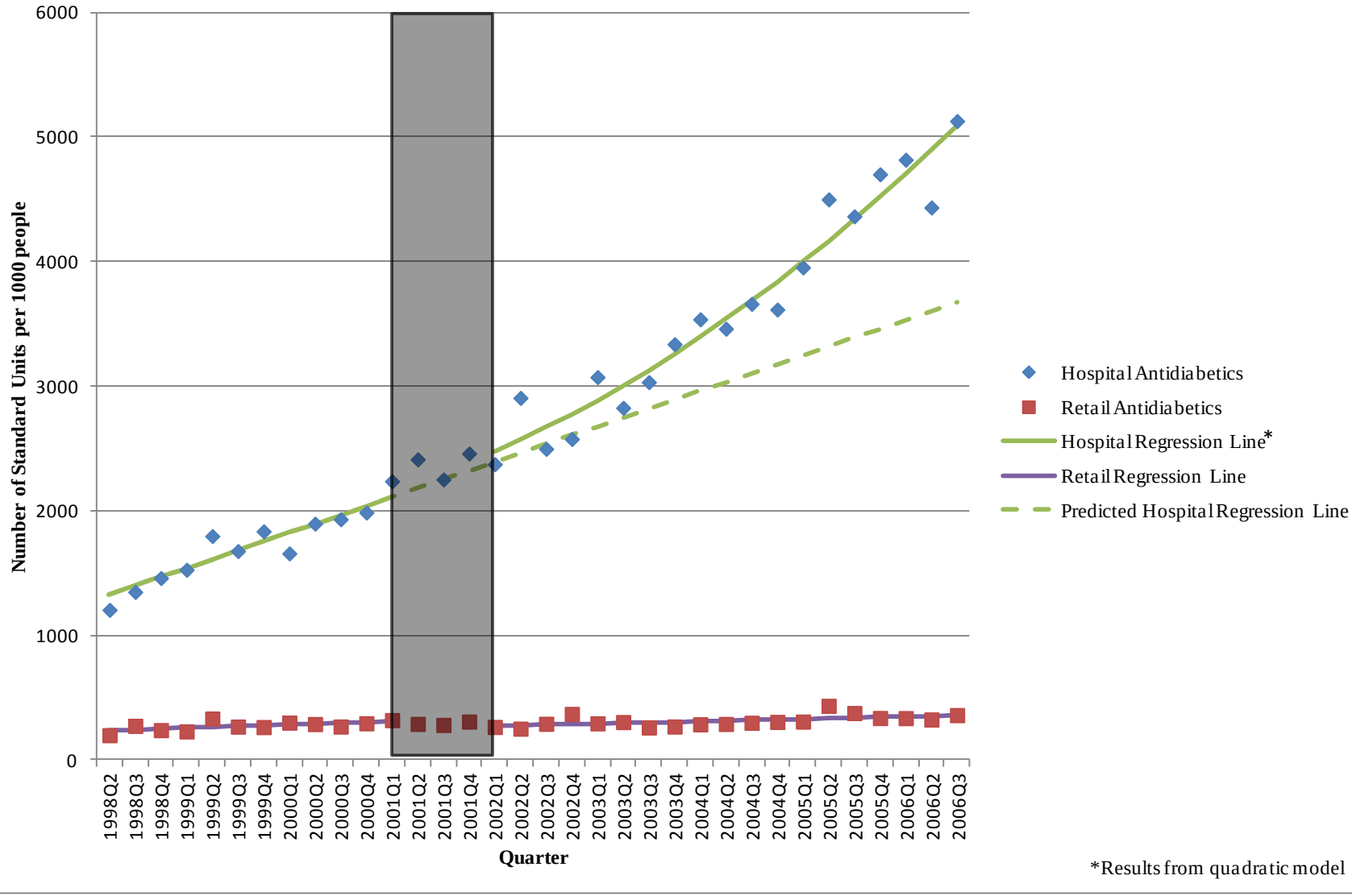
***All insulins were on NLEM (i.e., NLEM market share = 100%)

Appendix 1 Figure 1. Standard Units Per Capita by Quarter
Insulin (Hospital vs. Retail)



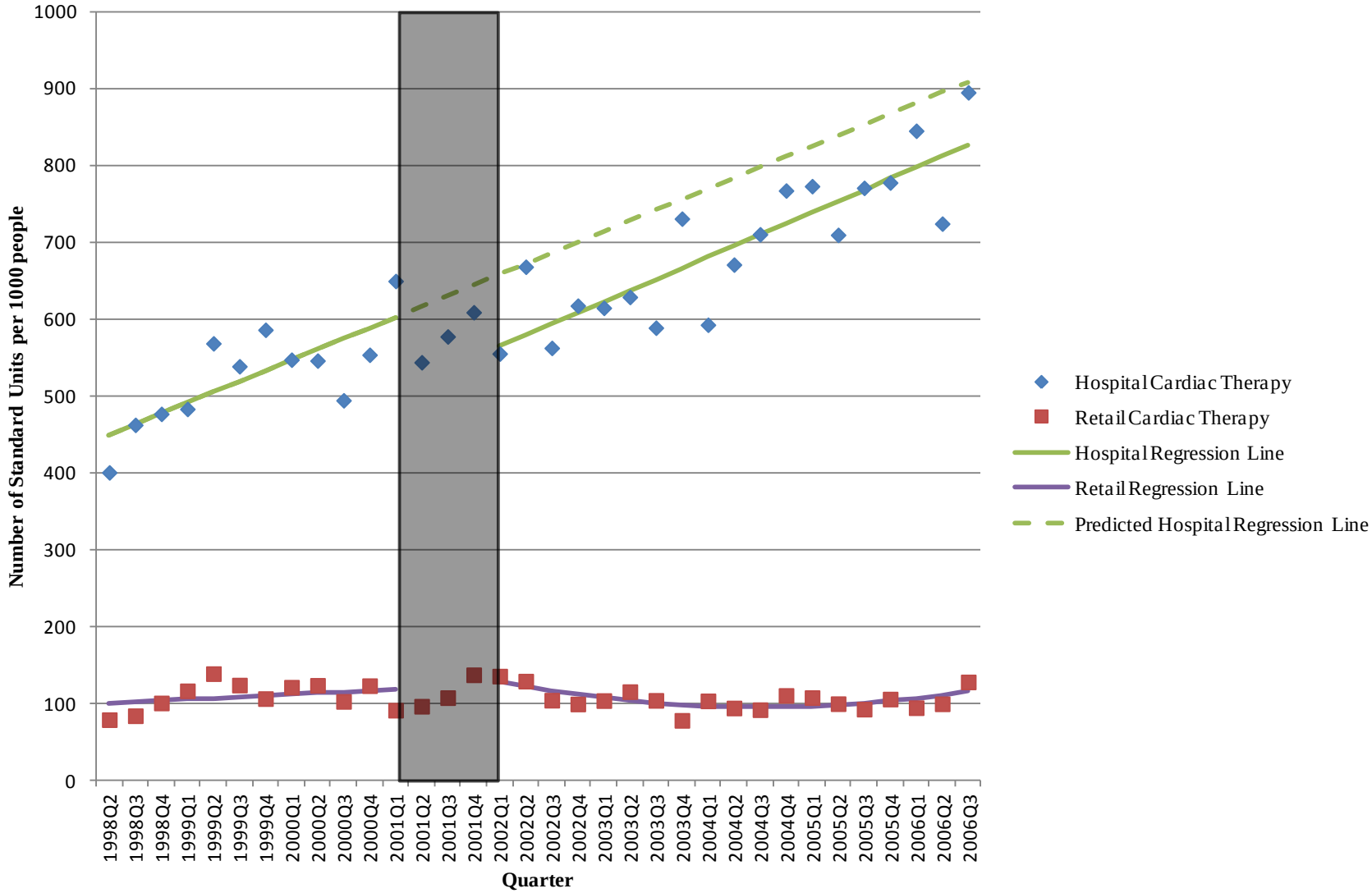
*Results from quadratic model

Appendix 1 Figure 2. Standard Units Per Capita by Quarter
Antidiabetics (Hospital vs. Retail)

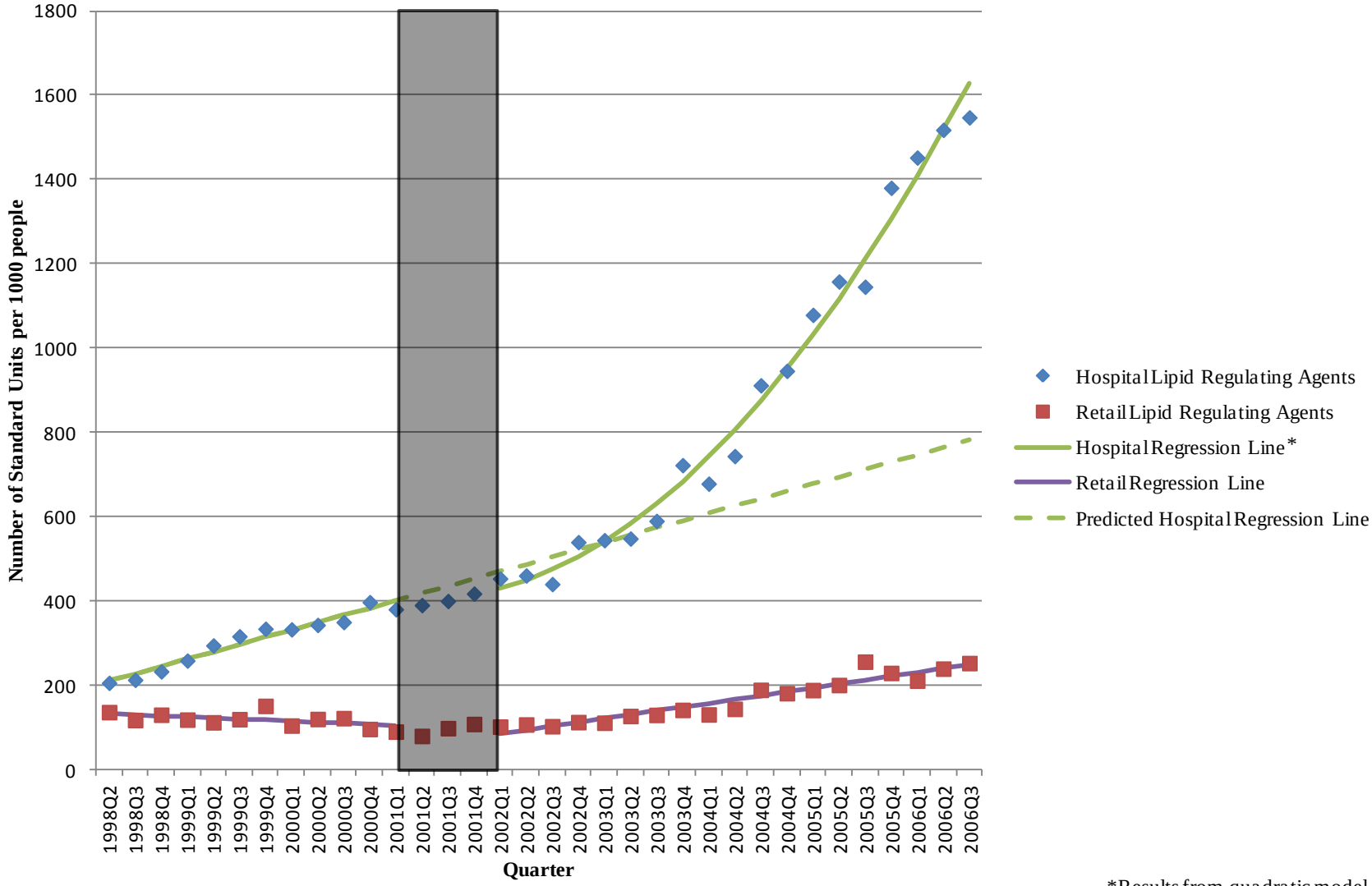


*Results from quadratic model

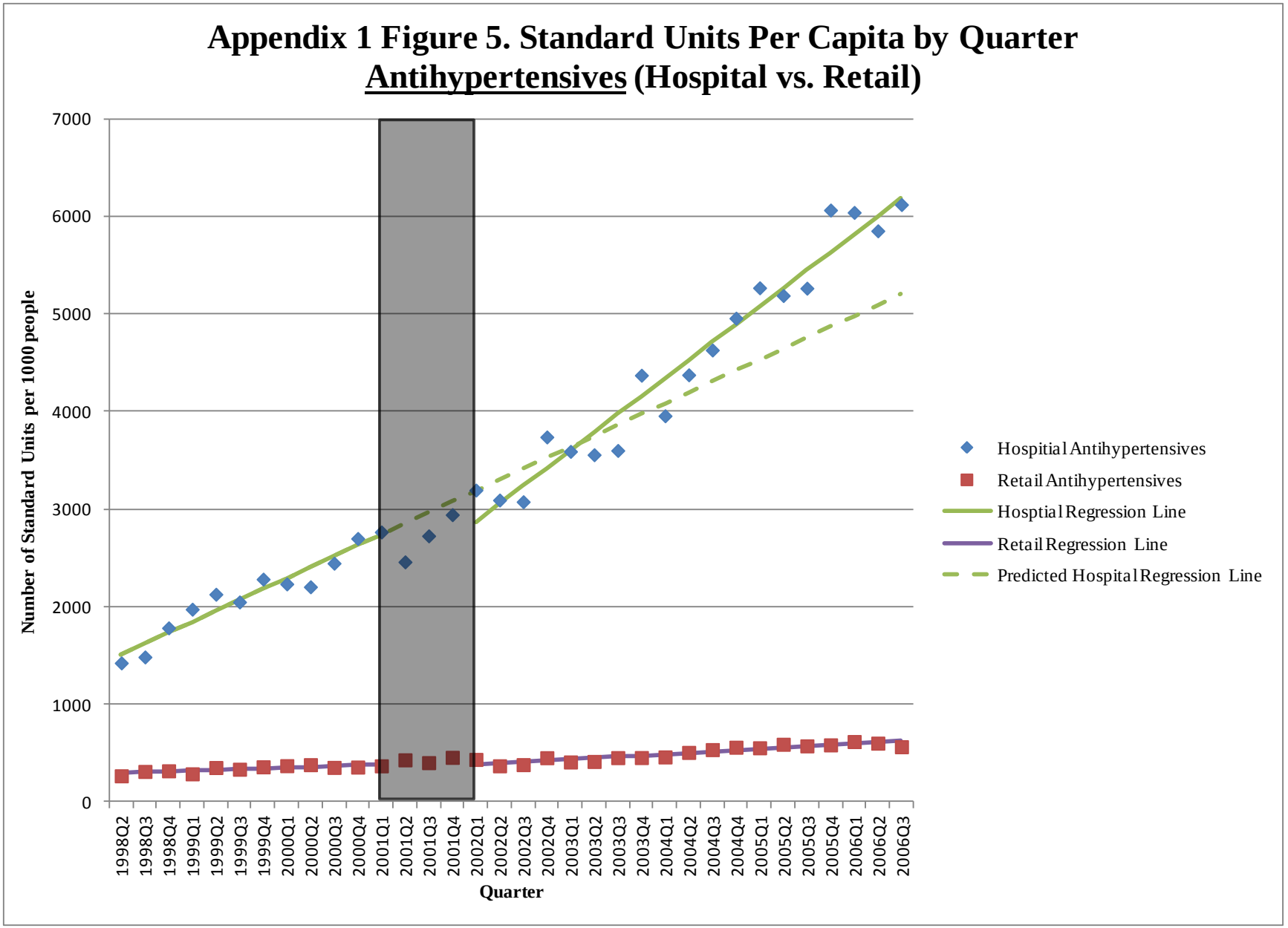
Appendix 1 Figure 3. Standard Units Per Capita by Quarter
Cardiac Therapy (Hospital vs. Retail)

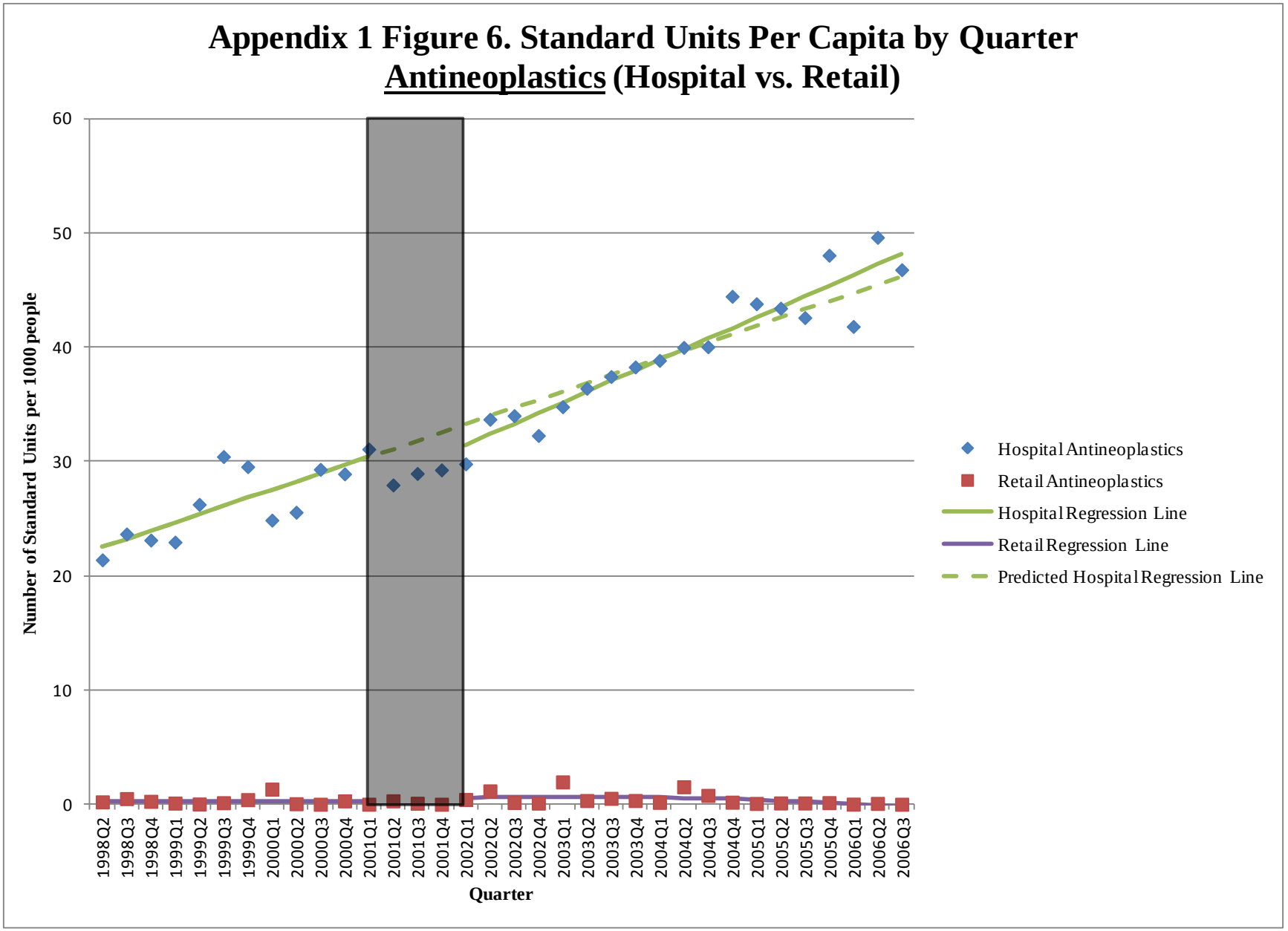


Appendix 1 Figure 4. Standard Units Per Capita by Quarter
Lipid Regulating Agents (Hospital vs. Retail)

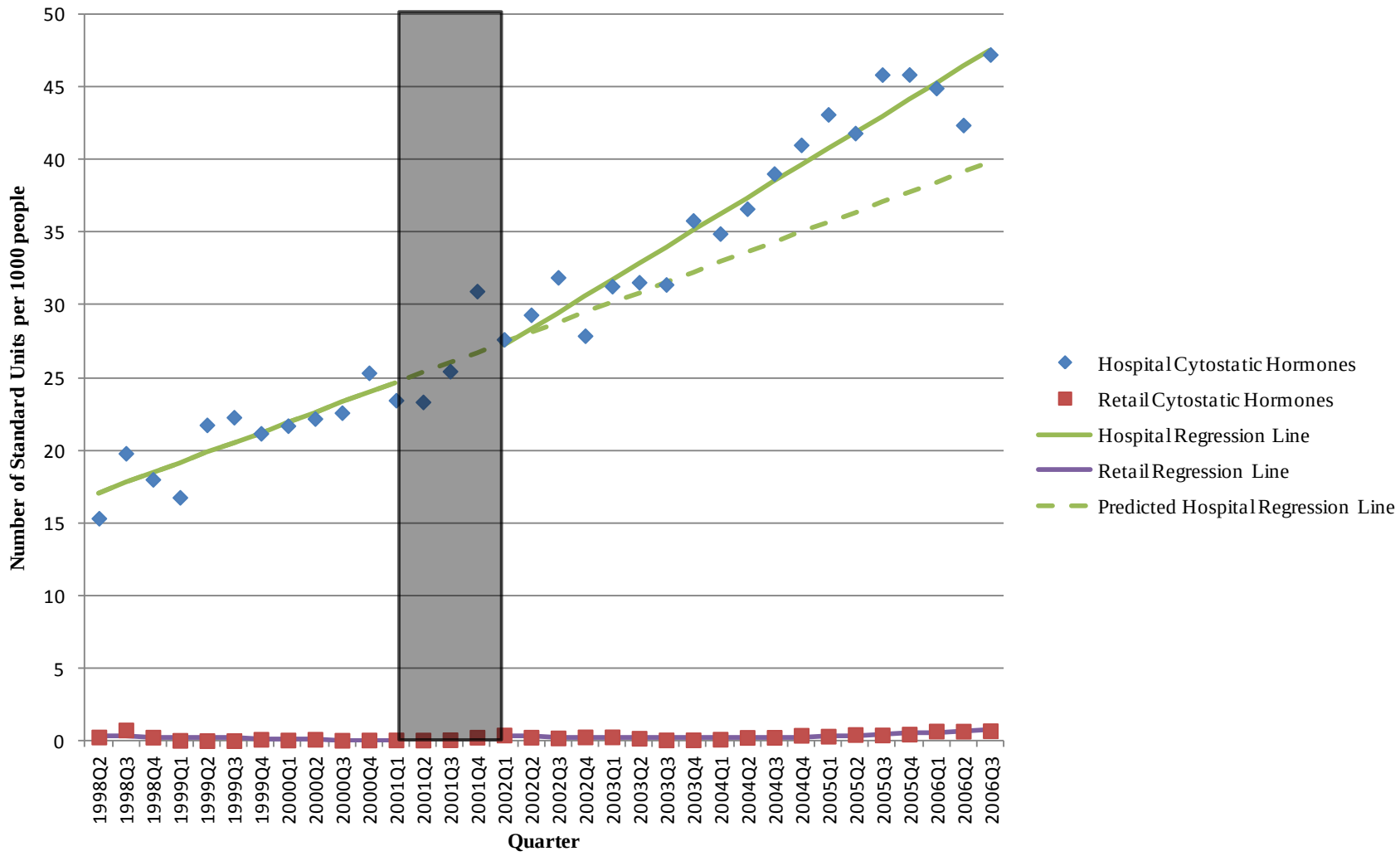


*Results from quadratic model

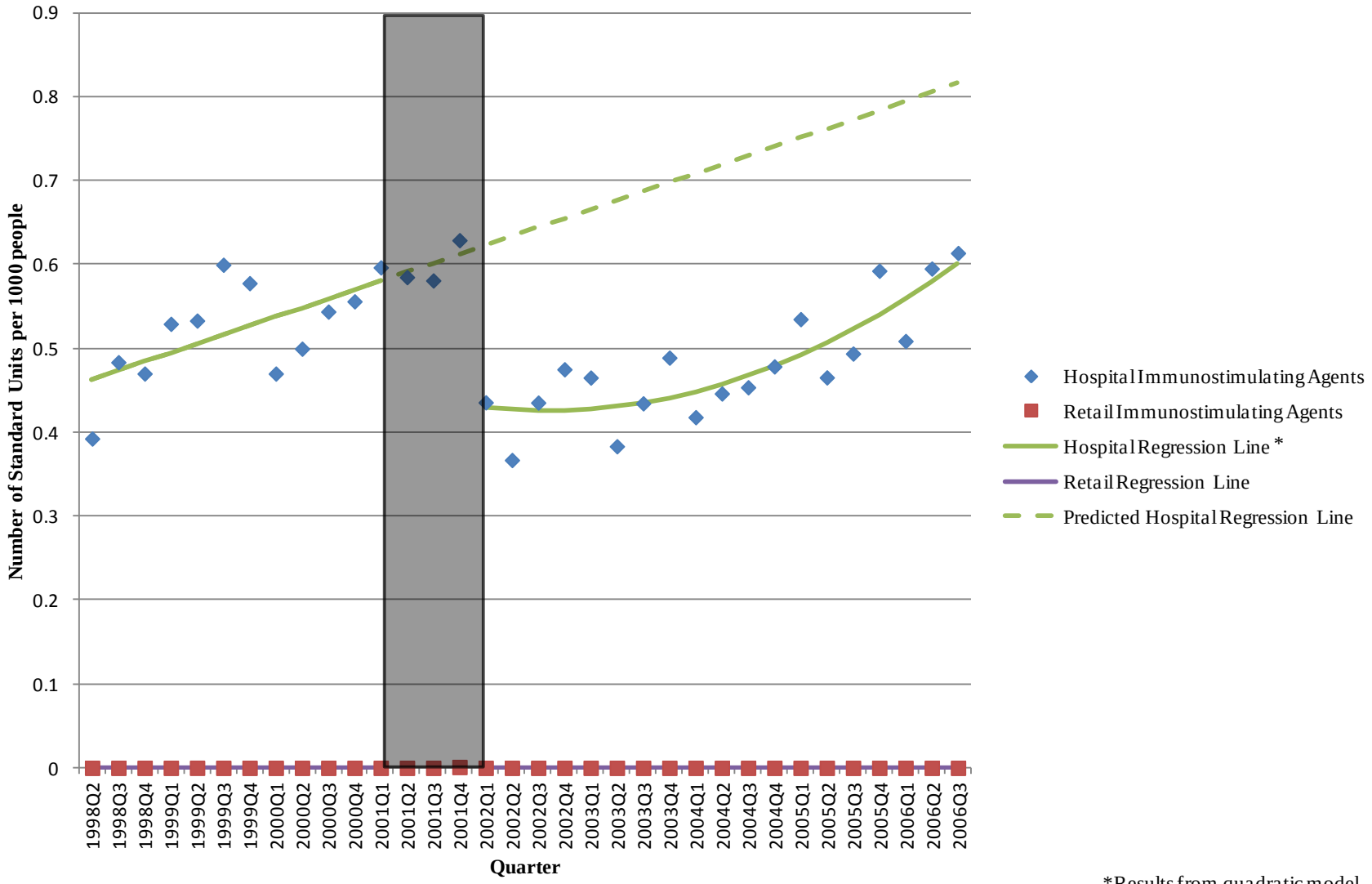

Appendix 1 Figure 5. Standard Units Per Capita by Quarter
Antihypertensives (Hospital vs. Retail)
Number of Standard Units per 1000 people
7000
6000
5000
4000
3000
2000
1000
0
1998Q2
1998Q3
1998Q4
1999Q1
1999Q2
1999Q3
1999Q4
2000Q1
2000Q2
2000Q3
2000Q4
2001Q1
2001Q2
2001Q3
2001Q4
2002Q1
2002Q2
2002Q3
2002Q4
2003Q1
2003Q2
2003Q3
2003Q4
2004Q1
2004Q2
2004Q3
2004Q4
2005Q1
2005Q2
2005Q3
2005Q4
2006Q1
2006Q2
2006Q3
Quarter
Hospitial Antihypertensives
Retail Antihypertensives
Hosptial Regression Line
Retail Regression Line
Predicted Hospital Regression Line


Appendix 1 Figure 6. Standard Units Per Capita by Quarter
Antineoplastics (Hospital vs. Retail)
Number of Standard Units per 1000 people
60
50
40
30
20
10
0
1998Q2
1998Q3
1998Q4
1999Q1
1999Q2
1999Q3
1999Q4
2000Q1
2000Q2
2000Q3
2000Q4
2001Q1
2001Q2
2001Q3
2001Q4
2002Q1
2002Q2
2002Q3
2002Q4
2003Q1
2003Q2
2003Q3
2003Q4
2004Q1
2004Q2
2004Q3
2004Q4
2005Q1
2005Q2
2005Q3
2005Q4
2006Q1
2006Q2
2006Q3
Quarter
Hospital Antineoplastics
Retail Antineoplastics
Hospital Regression Line
Retail Regression Line
Predicted Hospital Regression Line

Appendix 1 Figure 7. Standard Units Per Capita by Quarter
Cytostatic Hormones (Hospital vs. Retail)

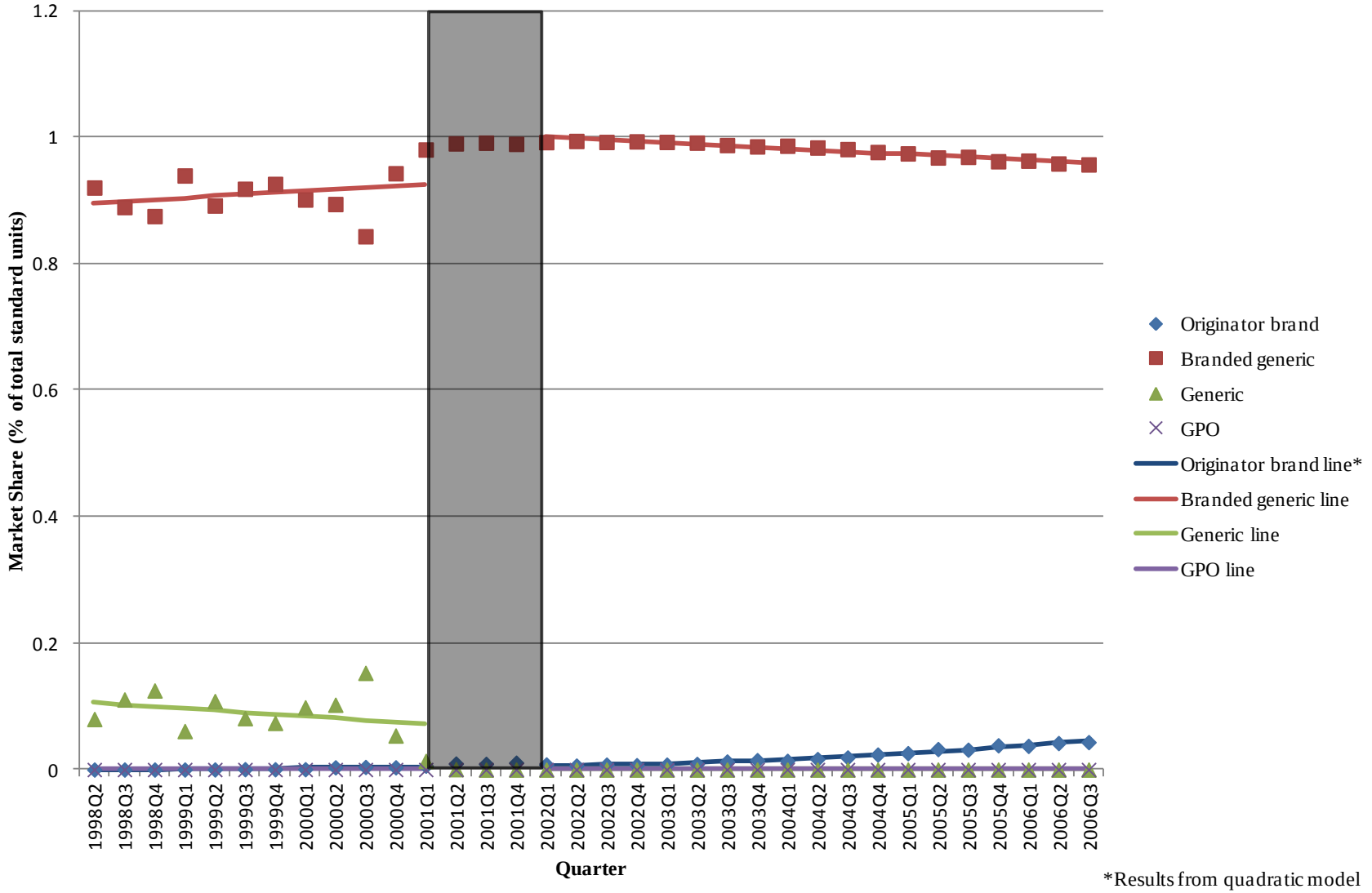


Appendix 1 Figure 8. Standard Units Per Capita by Quarter
Immunostimulating Agents (Hospital vs. Retail)



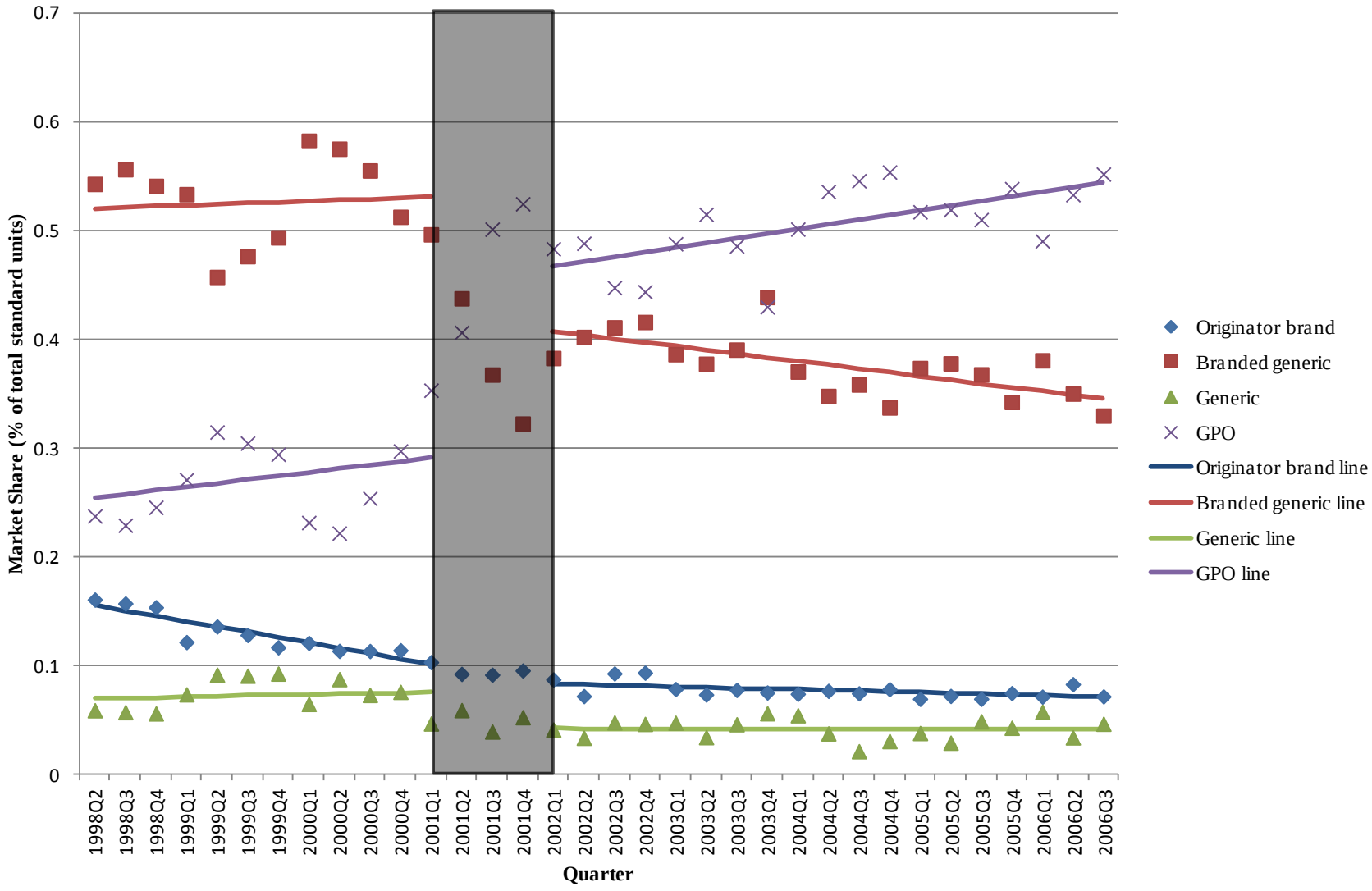
*Results from quadratic model

Appendix 1 Figure 9. Licensing Status Market Share by Quarter
Insulin (Hospital Sector)

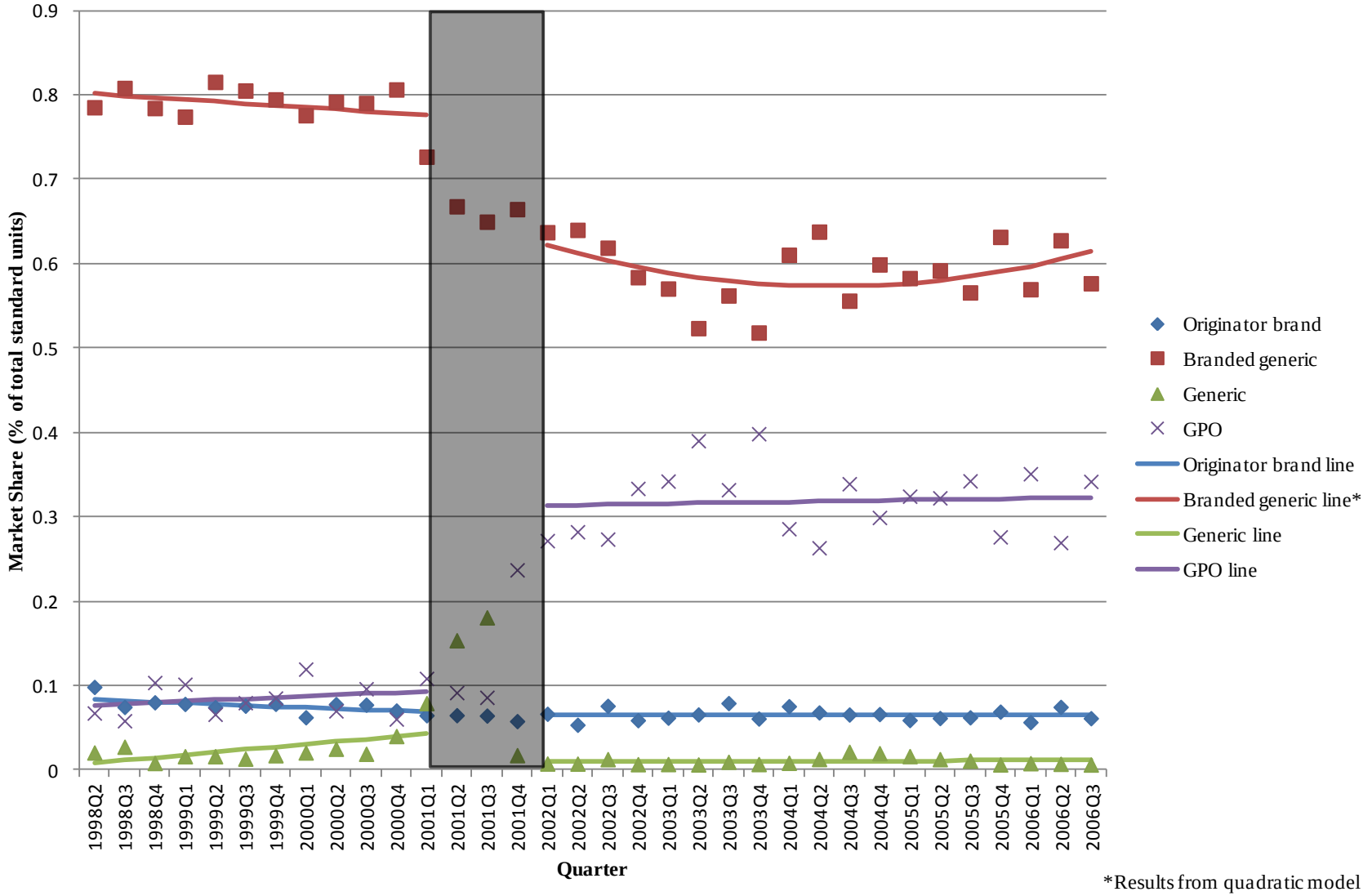


*Results from quadratic model

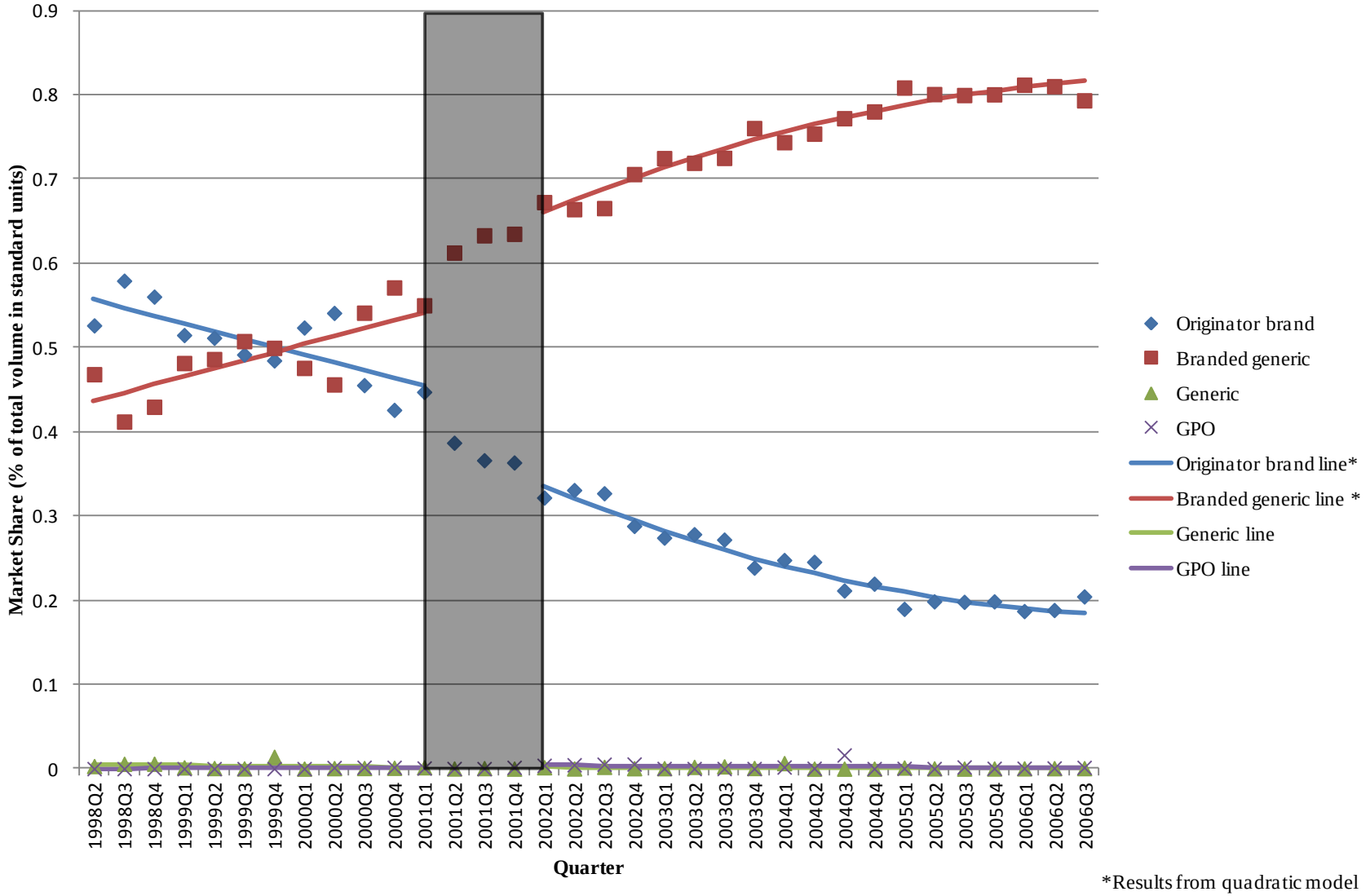
Appendix 1 Figure 10. Licensing Status Market Share by Quarter
Antidiabetics (Hospital Sector)



Appendix 1 Figure 11. Licensing Status Market Share by Quarter
Cardiac Therapy Agents (Hospital Sector)

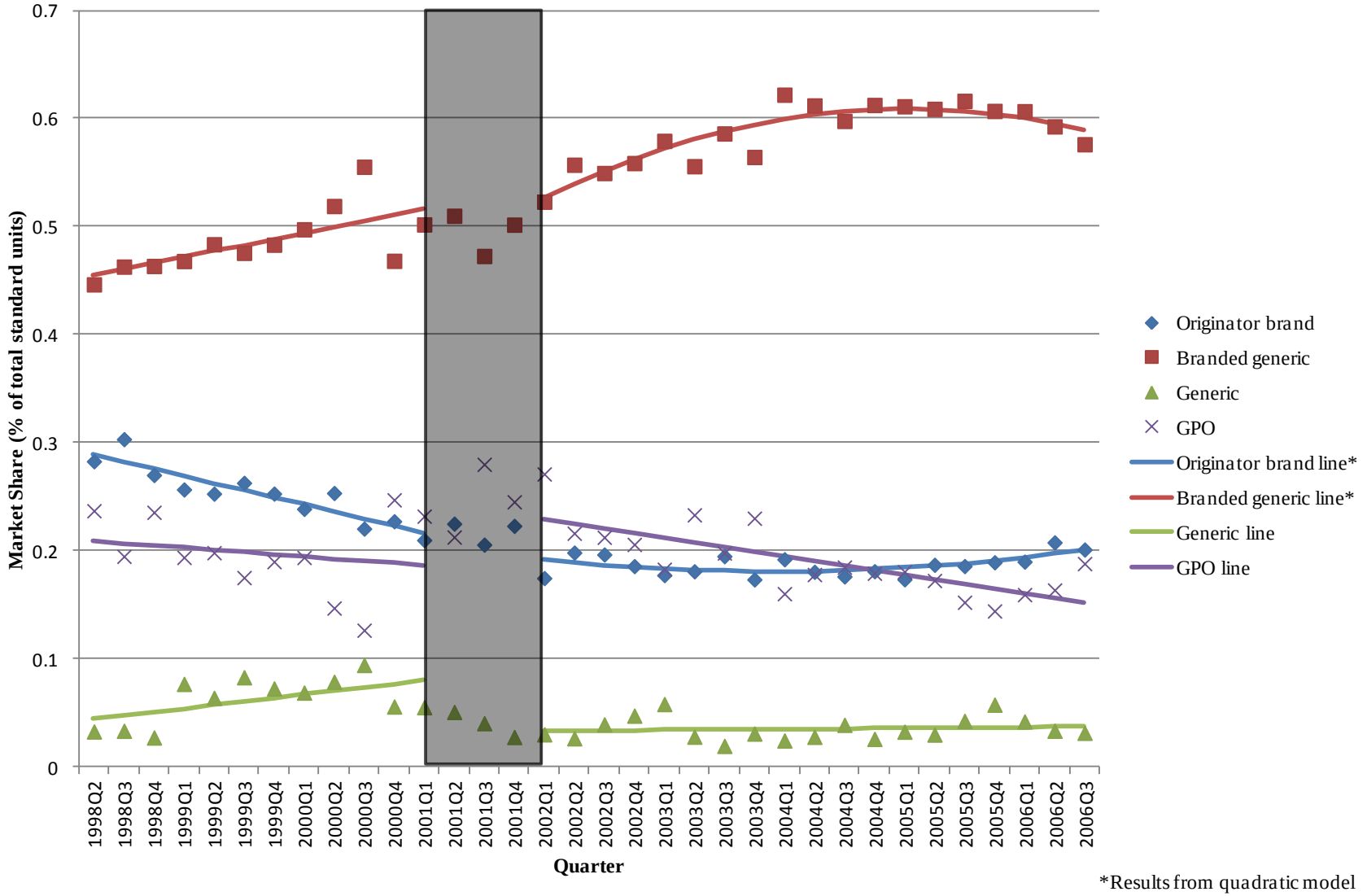


Appendix 1 Figure 12. Licensing Status Market Share by Quarter
Lipid Regulating Agents (Hospital Sector)



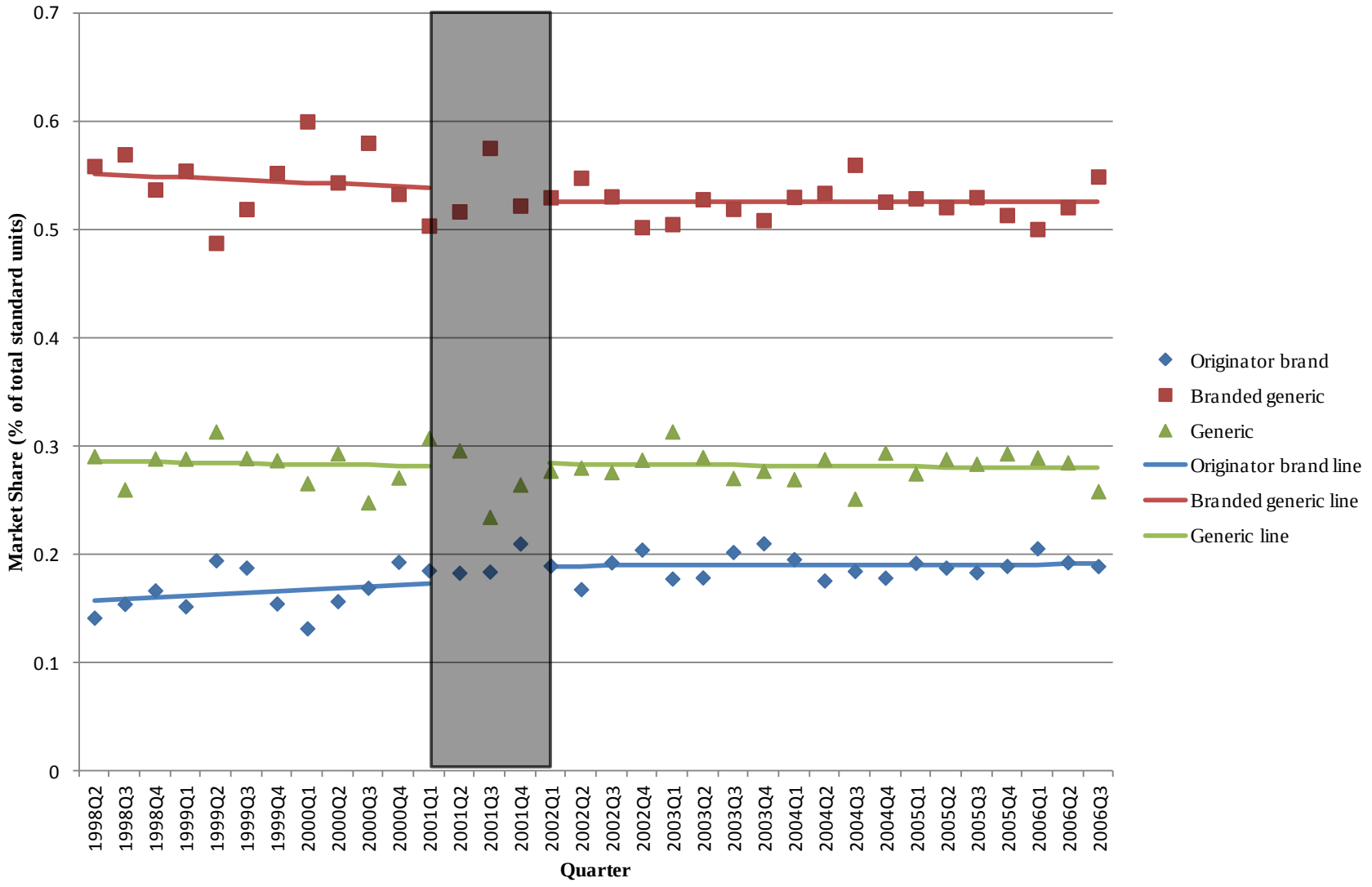
*Results from quadratic model

Appendix 1 Figure 13. Licensing Status Market Share by Quarter
Antihypertensives (Hospital Sector)

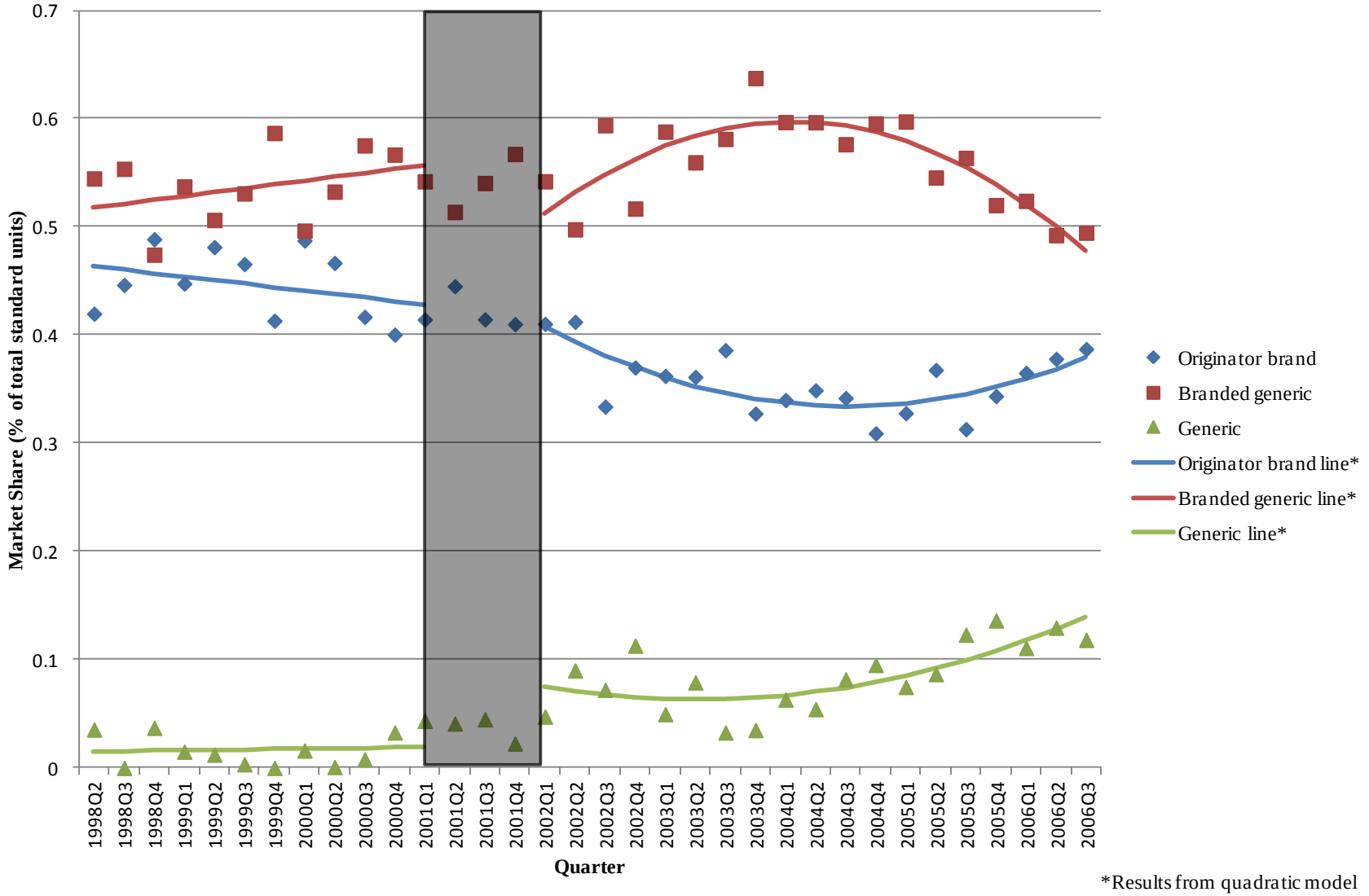


*Results from quadratic model

Appendix 1 Figure 14. Licensing Status Market Share by Quarter
Antineoplastics (Hospital Sector)

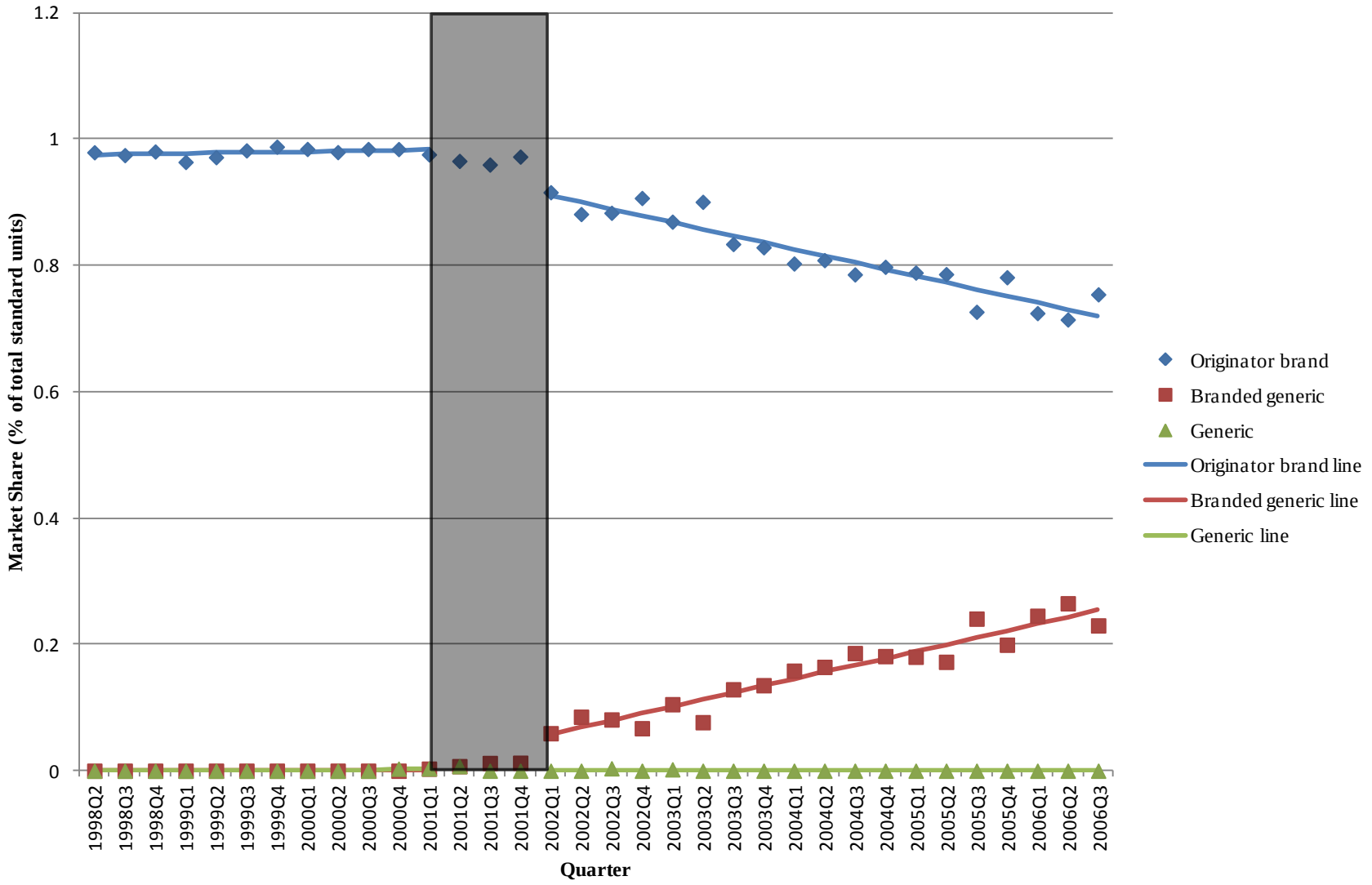


Appendix 1 Figure 15. Licensing Status Market Share by Quarter
Cytostatic Hormones (Hospital Sector)

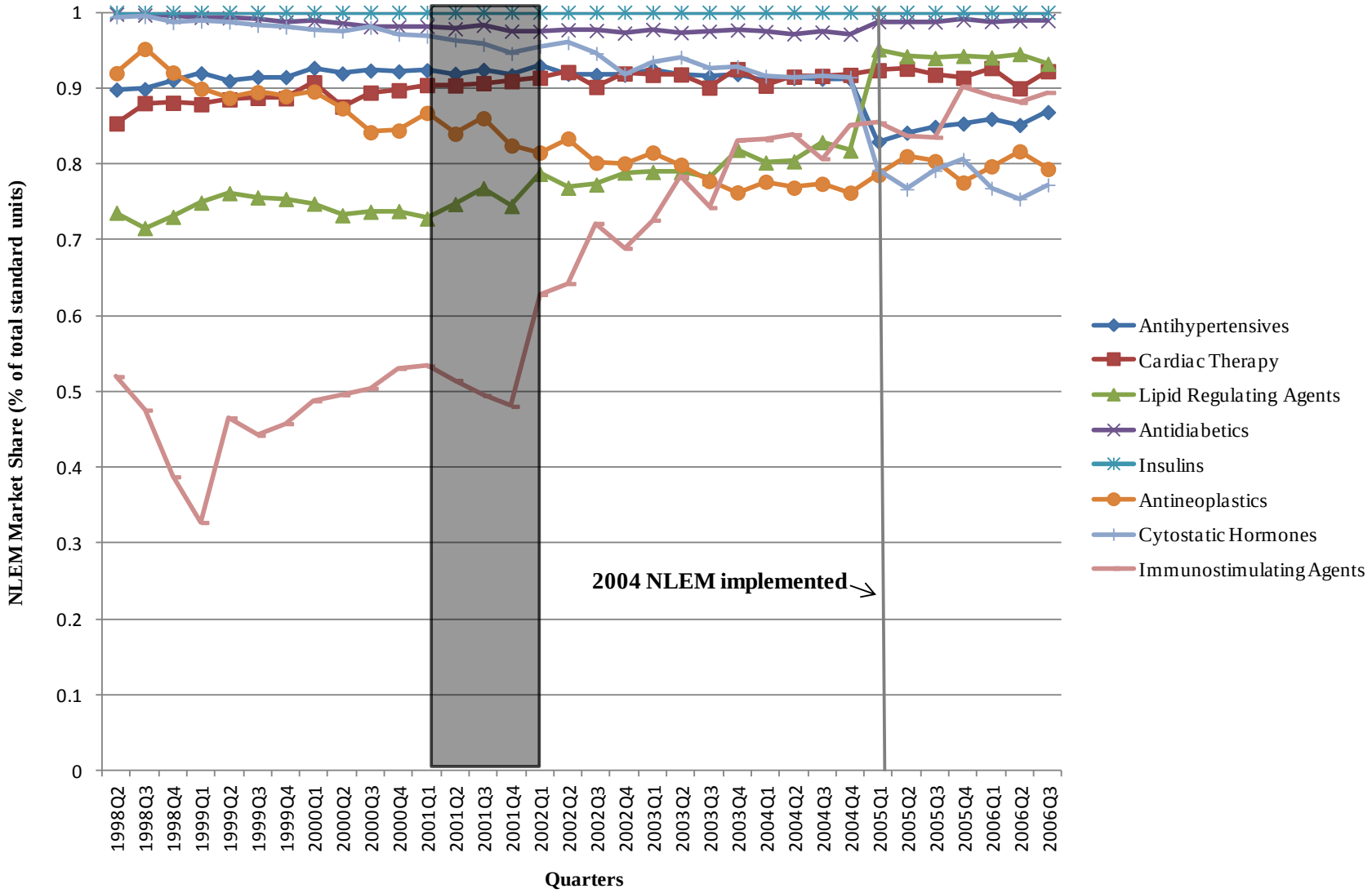


*Results from quadratic model

Appendix 1 Figure 16. Licensing Status Market Share by Quarter
Immunostimulating Agents (Hospital Sector)



Appendix 1 Figure 17. NLEM Market Share by Quarter (1999 and 2004 NLEM, raw data)



Chapter 2 Appendices

Appendix 2 Table 1. Demographic and Plan Characteristics, Pre vs. Post Reform (Adults, ages 18-64)

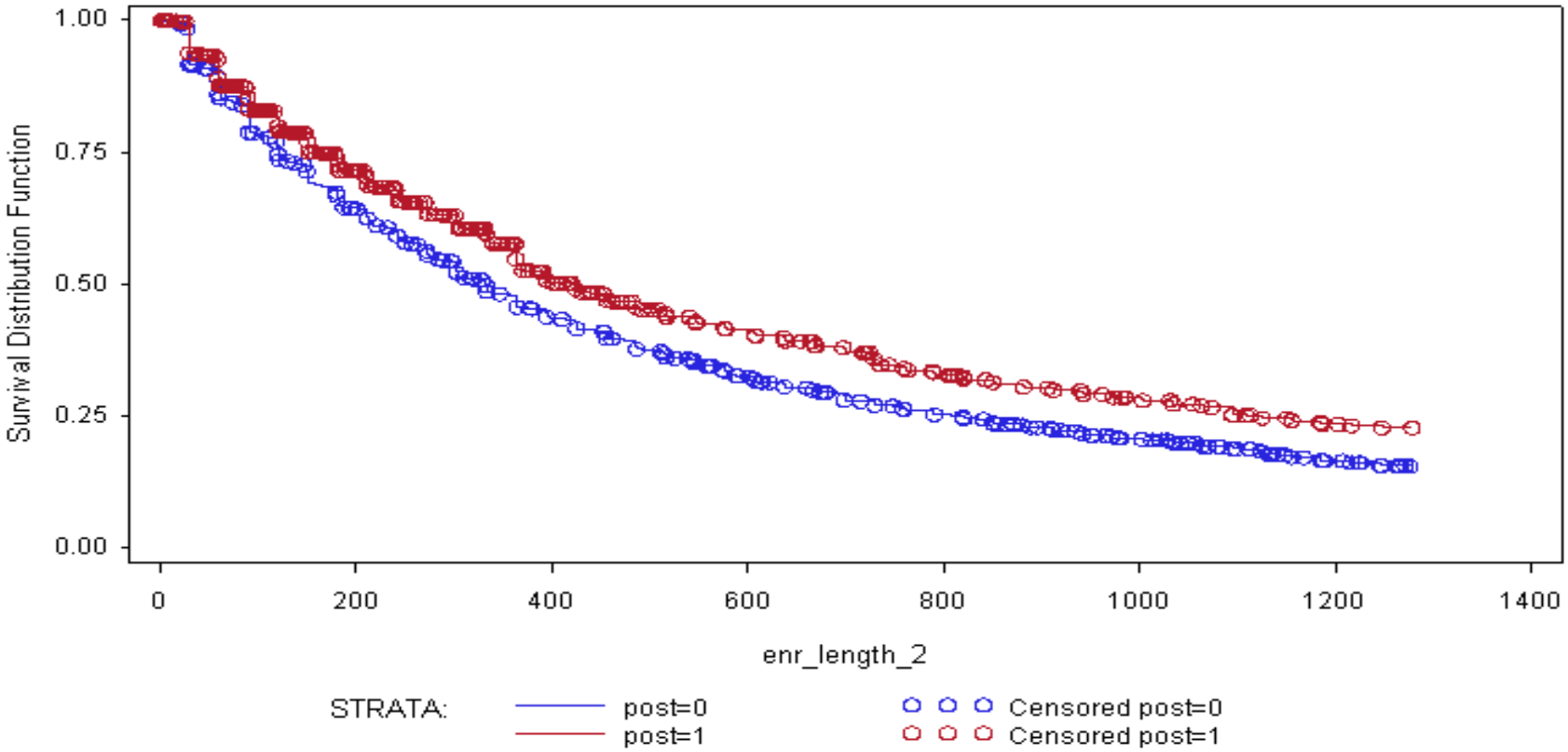
	Massachusetts - Individual Market (n=36,119)	
	Pre-Reform	***Post-Reform***
Number of Members	6,912	29,207
Gender (% male)	40.9	45.9**
Age (mean, std)	37.6 (13.7)	37.9 (14.0)
Age (distribution):		
Birth-17 years old	-	-
18-26 years old ("young adults")	29.8	31.6*
27-40 years old	32.5	27.2**
41-50 years old	14.9	17.2**
51-64 years old	22.9	24.0*
Race (mean % white, non-hispanic, std) *a*	87.4 (15.8)	88.7 (15.8)**
Education Level (mean % with at least some college, std) *a*	53.5 (19.7)	50.9 (19.1)**
Education Level Categories (mean %) *a*		
Less than 9th grade	3.4 (4.5)	3.5 (4.8)
9th - 12th grade	6.2 (5.1)	6.5 (5.2)**
High school graduate	21.4 (10.9)	22.7 (10.6)**
Some college, no degree	15.5 (6.0)	16.4 (6.0)**
Associate degree	6.5 (3.4)	7.0 (3.5)**
Bachelor degree	25.5 (9.4)	24.8 (9.5)**
Graduate or professional degree	21.5 (14.4)	19.2 (13.3)**
Family Income *a*		
Mean % Family Income <$50,000 (std)	30.2 (16.8)	31.4 (17.0)**
Mean % Family Income $50,000-$99,000 (std)	37.2 (12.2)	38.3 (12.2)**
Mean % Family Income >$100,000 (std)	33.6 (20.0)	30.2 (19.5)**
Primary Member (% who were subscriber)	90.2	77.6**
Dependent Member		
Spouse (% who are married to subscriber)	8.5	16.9**
Child (% who are a adult child of subscriber)	1.3	5.6**
Contract Type		
Individual (% of members in individual plan)	79.8	56.8**
Family (% of members in plan with at least one other person)	20.2	43.2**
Connector (% in Connector plan, post-reform only)	NA	60.90
Plan Characteristics		
HMO (% in HMO plan)	100	88.2**
PPO (% in PPO plan)	0.1	12.0**
HDHP (% in HDHP)	0	7.1**
Prescription Drug Coverage (% with Rx Benefit)	43.4	83.5**
Mental Health Coverage (% with MH coverage)	100	100

[a] % in census block of residence (education is % of population age 25+ in that level)

* post significantly different than pre (using chi-sq for categorical and t-test for continuous variables): $p<0.05$

** post significantly different than pre (using chi-sq for categorical and t-test for continuous variables): $p<0.0001$

Appendix 2 Figure 1. Time to Disenrollment – MA Individual Market Pre vs. Post-Reform (Adults)



Appendix 2 Table 2. Segmented Regression Models: Probability of Disenrollment by Month of Enrollment

Enrollment Length	Intercept	Pre-reform Trend (std. err.)	Immediate Post-Reform Level Change (std. err.)	Post-Reform Trend (std. err.)
≤ 45 days	0.071	0.000883 (0.000361)*	-0.0454(0.0115)*	-0.001031 (0.000531)
≤ 90 days	0.1606	0.001418 (0.000605)*	-0.0526 (0.0183)*	-0.002283 (0.000914)*
≤ 180 days	0.2896	0.002424 (0.001196)	-0.1035 (0.0296)*	-0.003366 (0.001851)
≤ 1 year	0.5193	0.001895 (0.000869)*	-0.0750 (0.0299)*	-0.003468 (0.001162)*

*p<0.05

Appendix 2 Table 3. Cox Proportional Hazard Models: Time to Disenrollment Pre vs. Post Reform

Parameter	Model 1: Univariate			Model 2: Demographic and Plan Characteristics			Model 3: With significant interaction terms		
	Estimate	*Hazard Ratio (95% CI)*	*p value*	*Estimate*	*Hazard Ratio (95% CI)*	*p value*	*Estimate*	*Hazard Rat*	*p value*
Post	-0.23737	**0.789 (0.764, 0.815)**	<.0001	-0.20955	**0.811 (0.784, 0.838)**	<.0001	-0.14841	.	0.1728
Female				0.08554	1.089 (1.059, 1.120)	<.0001	0.08679	1.091	<.0001
Age 18-26				0.74979	2.117 (2.032, 2.205)	<.0001	0.74945	2.116	<.0001
Age 27-40				0.58275	1.791 (1.718, 1.867)	<.0001	0.46832	.	<.0001
Age 41-50				0.28521	1.33 (1.264, 1.399)	<.0001	0.18666	.	<.0001
College Education				-0.03044	0.97 (0.869, 1.083)	0.5872	0.11552	.	0.1764
White, non-hispanic				-0.36236	0.696 (0.633, 0.766)	<.0001	-0.13826	.	0.1391
Family Income 50-100k				0.07812	1.081 (0.939, 1.245)	0.2783	0.08876	1.093	0.2184
Family Income > 100k				-0.2646	0.768 (0.676, 0.871)	<.0001	-0.26508	0.767	<.0001
Individual Plan				0.1467	1.158 (1.120, 1.197)	<.0001	-0.08301	.	0.0249
post*age_27to40							0.14832	.	<.0001
post*age_41to50							0.15079	.	0.0033
post*education_colle							-0.18476	.	0.0311
post*ra_nhs_wh							-0.29509	.	0.0043
post*Individual							0.28388	.	<.0001

Note: Enrollment analysis excludes children (ages 0-17); follow-up time = 3.5 years max in pre and post period
Reference groups:
Age reference group = Age 51-65
Education reference group = less than college education
Race reference group = all other races
Income reference group = family income less than 50k

Model includes interaction terms that were significant after stepwise removal of non-significant interaction terms

Appendix 2 Table 4. Cox Proportional Hazard Models: Time to Disenrollment Pre vs. Post Reform (Stratified Analyses)

Model	Post (vs. Pre) Reform Hazard Ratio (95% CI)
Univariate Model	0.789 (0.764, 0.815)
Multivariate Models[a]	
Entire Study Population	0.811 (0.784, 0.838)
Age 18-26	0.841 (0.796, 0.890)
Age 27-40	0.852 (0.852, 0.902)
Age 41-50	0.770 (0.695, 0.852)
Age 51-64	0.709 (0.657, 0.766)
College Education (>51% with)[b]	0.791 (0.755, 0.830)
No College Education (≤51% with college education)[b]	0.838 (0.800, 0.879)
White, non-hispanic (>88% white)[b]	0.781 (0.749, 0.814)
All other races (≤88% white)[b]	0.859 (0.813, 0.907)
Individual Plan	0.854 (0.822, 0.887)
Family Plan	0.681 (0.636, 0.730)

[a]Multivariate models control for: sex, age, education, race, family income, and individual/family plan. Models stratified by covariates with significant post*covariate interaction terms.

[b]Percents correspond to a % in census block of residence. Dichotomous categories created by dividing continuous variable at mean of study population.

Appendix 2 Table 5. Cox Proportional Hazard Models: Time to First Medical Encounter By Encounter Type, Pre vs. Post Reform

	Encounter Type											
Parameter	**Ambulatory**			**Emergency Department**			**Inpatient**			**Same Day Surgery**		
	Estimate	**Hazard Ratio (95% CI)**	**p value**	**Estimate**	**Hazard Ratio (95% CI)**	**p value**	**Estimate**	**Hazard Ratio (95% CI)**	**p value**	**Estimate**	**Hazard Ratio (95% CI)**	**p value**
Post	0.03589	**1.037 (1.004, 1.070)**	0.026	-0.16165	**0.851 (0.795, 0.911)**	<.0001	-0.18559	**0.831 (0.744, 0.927)**	0.001	-0.05064	0.951 (0.842, 1.073)	0.4139
Female	0.49497	1.64 (1.600, 1.682)	<.0001	-0.01853	0.982 (0.928, 1.038)	0.5162	0.5089	1.663 (1.509, 1.834)	<.0001	0.28106	1.325 (1.197, 1.465)	<.0001
Age 18-26	-0.49973	0.607 (0.587, 0.628)	<.0001	0.15268	1.165 (1.080, 1.257)	<.0001	-0.46255	0.63 (0.548, 0.724)	<.0001	-1.01913	0.361 (0.309, 0.421)	<.0001
Age 27-40	-0.24128	0.786 (0.760, 0.812)	<.0001	0.13581	1.145 (1.061, 1.236)	0.0005	0.33541	1.399 (1.249, 1.565)	<.0001	-0.34727	0.707 (0.624, 0.800)	<.0001
Age 41-50	-0.17297	0.841 (0.810, 0.874)	<.0001	-0.00303	0.997 (0.910, 1.092)	0.9482	-0.35964	0.698 (0.598, 0.815)	<.0001	-0.19967	0.819 (0.712, 0.942)	0.0051
College Education	-0.19354	0.824 (0.746, 0.911)	0.0001	-0.63347	0.531 (0.422, 0.668)	<.0001	-0.90566	0.404 (0.275, 0.595)	<.0001	-0.22757	0.796 (0.527, 1.204)	0.2808
White, non-hispanic	0.098	1.103 (1.004, 1.211)	0.04	0.17519	1.191 (0.966, 1.469)	0.1014	-0.20886	0.812 (0.582, 1.131)	0.2176	-0.03581	0.965 (0.660, 1.410)	0.8532
Family Income 50-100k	0.0462	1.047 (0.922, 1.190)	0.4772	-0.05602	0.946 (0.710, 1.259)	0.7015	0.17357	1.19 (0.737, 1.920)	0.4771	0.17906	1.196 (0.714, 2.002)	0.4958
Family Income > 100k	0.2487	1.282 (1.145, 1.436)	<.0001	0.01957	1.02 (0.785, 1.324)	0.8832	0.51692	1.677 (1.082, 2.600)	0.0208	-0.04187	0.959 (0.601, 1.529)	0.8604
Individual Plan	0.08104	1.084 (1.054, 1.115)	<.0001	0.12324	1.131 (1.060, 1.207)	0.0002	-0.01323	0.987 (0.891, 1.093)	0.8002	0.07437	1.077 (0.965, 1.202)	0.1851

Appendix 2 Table 6. Cox Proportional Hazard Models: Time to First Medical Encounter By Encounter Type, Pre vs. Post Reform (with significant interaction terms)

	Encounter Type											
	Ambulatory			Emergency Department			Inpatient			Same Day Surgery		
Parameter	Estimate	Hazard Ratio (95% CI)	p value	Estimate	Hazard Ratio (95% CI)	p value	Estimate	Hazard Ratio (95% CI)	p value	Estimate	Hazard Ratio (95% CI)	p value
Post	-0.009	.	0.7736	0.06947	.	0.54	0.24301	.	0.1925	-0.05064	0.951	0.4139
Female	0.49579	1.642	<.0001	-0.01881	0.981	0.51	0.51014	1.666	<.0001	0.28106	1.325	<.0001
Age												
Age 18-26	-0.3726	.	<.0001	0.15373	1.166	<.0001	-0.20402	.	0.1122	-1.01913	0.361	<.0001
Age 27-40	-0.23822	0.788	<.0001	0.13664	1.146	0.0004	0.33827	1.403	<.0001	-0.34727	0.707	<.0001
Age 41-50	-0.17231	0.842	<.0001	-0.00175	0.998	0.9701	-0.35816	0.699	<.0001	-0.19967	0.819	0.0051
College Education	-0.19846	0.82	<.0001	-0.63264	0.531	<.0001	-0.91338	0.401	<.0001	-0.22757	0.796	0.2808
White, non-hispanic	0.09991	1.105	0.0365	0.17383	1.19	0.104	-0.21353	0.808	0.2073	-0.03581	0.965	0.8532
Family Income 50-100k	0.04215	1.043	0.5169	0.41575	.	0.114	0.91705	.	0.0304	0.17906	1.196	0.4958
Family Income > 100k	0.04001	.	0.6388	0.02483	1.025	0.8521	0.52988	1.699	0.0178	-0.04187	0.959	0.8604
Individual Plan	0.0862	1.09	<.0001	0.12362	1.132	0.0002	-0.00976	0.99	0.8522	0.07437	1.077	0.1851
Post*Female	-	-	-	-	-	-	-	-	-	-	-	-
Post*Age												
Post*Age 18-26	-0.15488	-	<.0001	-	-	-	-0.33251	-	0.0192	-	-	-
Post*Age 27-40	-	-	-	-	-	-	-	-	-	-	-	-
Post*Age 41-50	-	-	-	-	-	-	-	-	-	-	-	-
Post*College Education	-	-	-	-	-	-	-	-	-	-	-	-
Post*White, non-hispanic	-	-	-	-	-	-	-	-	-	-	-	-
Post*Family Income 50-100k	-	-	-	-0.60521	-	0.0311	-0.96876	-	0.0324	-	-	-
Post*Family Income > 100k	0.26331	-	0.0008	-	-	-	-	-	-	-	-	-
Post*Individual Plan	-	-	-	-	-	-	-	-	-	-	-	-

Models include interaction terms that were significant after stepwise removal of non-significant interaction terms.

Appendix 2 Table 7. Cox Proportional Hazard Models: Time to First Medical Encounter By Encounter Type, Pre vs. Post Reform (Stratified Analyses)[a]

	Post (vs. Pre) Reform Hazard Ratio (95% CI) by Encounter Type			
Stratified Model	**Ambulatory**	**Emergency Department**	**Inpatient**	**Infertility Treatment**
Age 18-26	**0.906 (0.853, 0.963)**	-	**0.619 (0.479, 0.801)**	-
Age 27-40	**1.084 (1.024, 1.147)**	-	**0.813 (0.686, 0.964)**	-
Age 41-50	**1.175 (1.076, 1.283)**	-	1.262 (0.887, 1.796)	-
Age 51-64	1.057 (0.995, 1.123)	-	0.946 (0.771, 1.161)	-
Income 50-100 (≤38%)[b]	-	0.933 (0.844, 1.032)	0.884 (0.753, 1.038)	-
Income 50-100 (>38%)[b]	-	**0.785 (0.716, 0.861)**	**0.769 (0.662, 0.895)**	-
Income >100 (≤31%)[b]	1.005 (0.963, 1.048)	-	-	-
Income >100 (>31%)[b]	**1.071 (1.022, 1.123)**	-	-	-
Individual Plan	-	-	-	**1.985 (1.529, 2.576)**
Family Plan	-	-	-	0.708 (0.339, 1.481)

[a]Stratified by covariate that had significant covariate*post interaction. Same Day Surgery and Knee Surgery models did not have any significant interactions.

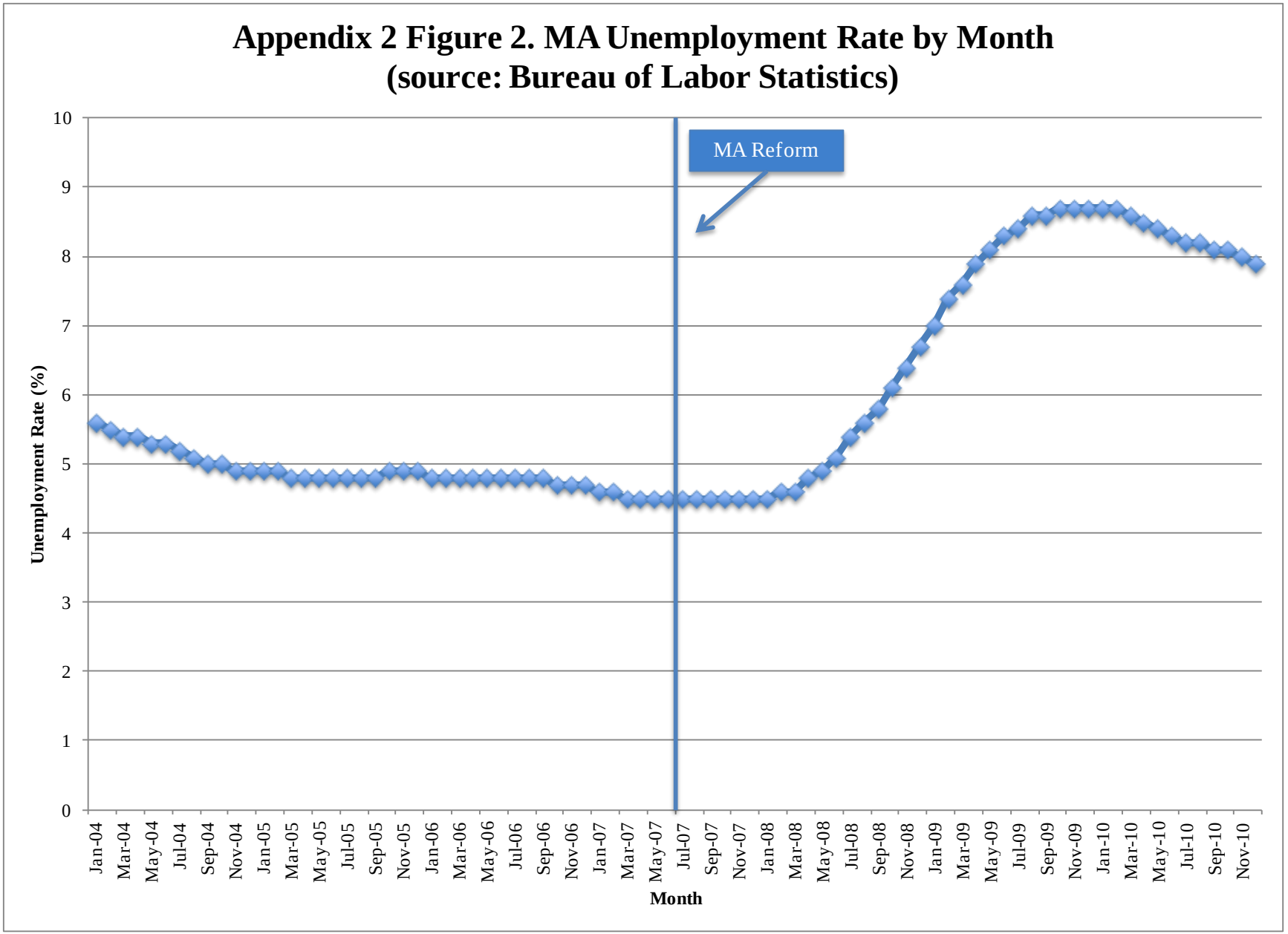
[b]Percents correspond to a % in census block of residence. Dichotomous categories created by dividing continuous variable at mean of study population.

Appendix 2 Table 8. Cox Proportional Hazard Models: Time to First Medical Encounter By Elective Encounter Type, Pre vs. Post Reform

	Elective Encounter Type					
Parameter	**Knee Surgery**			**Infertility Treatment**		
	Estimate	**Hazard Ratio (95% CI)**	**p value**	**Estimate**	**Hazard Ratio (95% CI)**	**p value**
Post	-0.16717	0.846 (0.600, 1.194)	0.3412	0.52894	**1.697 (1.325, 2.174)**	<.0001
Female	-0.46268	0.63 (0.476, 0.832)	0.0011	-	-	-
Age	-	-	-	-0.0044	0.996 (0.980, 1.011)	0.5829
Age 18-26	-0.731	0.481 (0.319, 0.727)	0.0005	-	-	-
Age 27-40	-0.51698	0.596 (0.407, 0.875)	0.0082	-	-	-
Age 41-50	0.09035	1.095 (0.758, 1.581)	0.6298	-	-	-
College Education	0.57211	1.772 (0.556, 5.646)	0.3333	-2.28566	0.102 (0.045, 0.231)	<.0001
White, non-hispanic	0.24985	1.284 (0.415, 3.969)	0.6644	-1.23126	0.292 (0.161, 0.528)	<.0001
Family Income 50-100k	-0.14735	0.863 (0.201, 3.713)	0.8431	1.63629	5.136 (1.820, 14.490)	0.002
Family Income > 100k	-0.66762	0.513 (0.141, 1.864)	0.3106	2.96698	19.433 (7.314, 51.636)	<.0001
Individual Plan	-0.09872	0.906 (0.663, 1.237)	0.5346	2.30475	10.022 (7.208, 13.934)	<.0001

Appendix 2 Table 9. Cox Proportional Hazard Models: Time to First Medical Encounter By Elective Encounter Type, Pre vs. Post Reform (with significant interactions)

	Encounter Type		
	Infertility Treatment		
Parameter	**Estimate**	**Hazard Ratio (95% CI)**	**p value**
Post	-0.66368	.	0.0755
Age	-0.00229	0.998	0.7753
College Education	-2.27621	0.103	<.0001
White, non-hispanic	-1.23053	0.292	<.0001
Family Income 50-100k	1.65302	5.223	0.0018
Family Income > 100k	2.97087	19.509	<.0001
Individual Plan	1.19613	.	0.0007
Post*Age	-	-	-
Post*College Education	-	-	-
Post*White, non-hispanic		-	-
Post*Family Income 50-100k	-	-	-
Post*Family Income > 100k		-	-
Post*Individual Plan	1.29485	.	0.0011


Appendix 2 Figure 2. MA Unemployment Rate by Month
(source: Bureau of Labor Statistics)
MA Reform
Unemployment Rate (%)
0
1
2
3
4
5
6
7
8
9
10
Month
Jan-04
Mar-04
May-04
Jul-04
Sep-04
Nov-04
Jan-05
Mar-05
May-05
Jul-05
Sep-05
Nov-05
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Mar-10
May-10
Jul-10
Sep-10
Nov-10

Chapter 3 Appendices

APPENDIX 3.1: SYSTEMATIC REVIEW STRATEGY TO IDENTIFY IV CER STUDIES

Databases Searched: PubMed, EconLit, PsychInfo, Social Services Abstracts, Social Sciences Citation Index and Web of Science

Search Terms:
("instrumental variable" OR "instrumental variables") AND ("health" OR "medicine" OR "medical" OR "disease" OR "patient" OR "patients" OR "care" OR "Medicare" OR "Medicaid" OR "obesity" OR "substance abuse" OR "epidemiology" OR "epidemiological" OR "epidemiologic" OR "fertility" OR "drug" OR "drugs" OR "medication")

APPENDIX 3.2: CONFOUNDER SEARCH TERMS AND STRATEGIES

SEARCH TERMS
Distance:
- "Distance"
- "Travel"
- "Rural"
- "Health Services Accessibility"[Mesh]
- "Geography"

Regional Variation:
-"Regional variation"
-"Geographic variation"
-"Area variation"
-"Hospital referral region"
-"Dartmouth Atlas"
-"Wennberg [Author]"
-"Fisher ES [Author]"

Facility Variation:
- Hospital: ("hospitals"[MeSH Terms] OR "hospitals" OR "hospital")
- "Variation"

Physician Variation:
-"Physician's Practice Patterns"[Mesh]
-"Physician"
-"Provider"
-"Variation"

Outcomes:
- "Mortality"[MeSH]
- "Health Status"[Mesh]
- "Health Status Indicators"[Mesh]

- "Health Status Disparities"[Mesh]
- "Outcome Assessment (Health Care)"[Mesh]

Disease-specific (for popular IV CER topics):
Cardiovascular: ("Heart Failure"[Mesh] or "acute myocardial infarction" or "stroke")
Antipsychotics: "Antipsychotic Agents"[Mesh]

Other search terms:
-"English[lang]"
-"Volume"

[Note: We used combinations of the above search terms. Given the qualitative and non-systematic nature of the search for confounders, this is not an exhaustive list of all search terms.]

SEARCH STRATEGIES

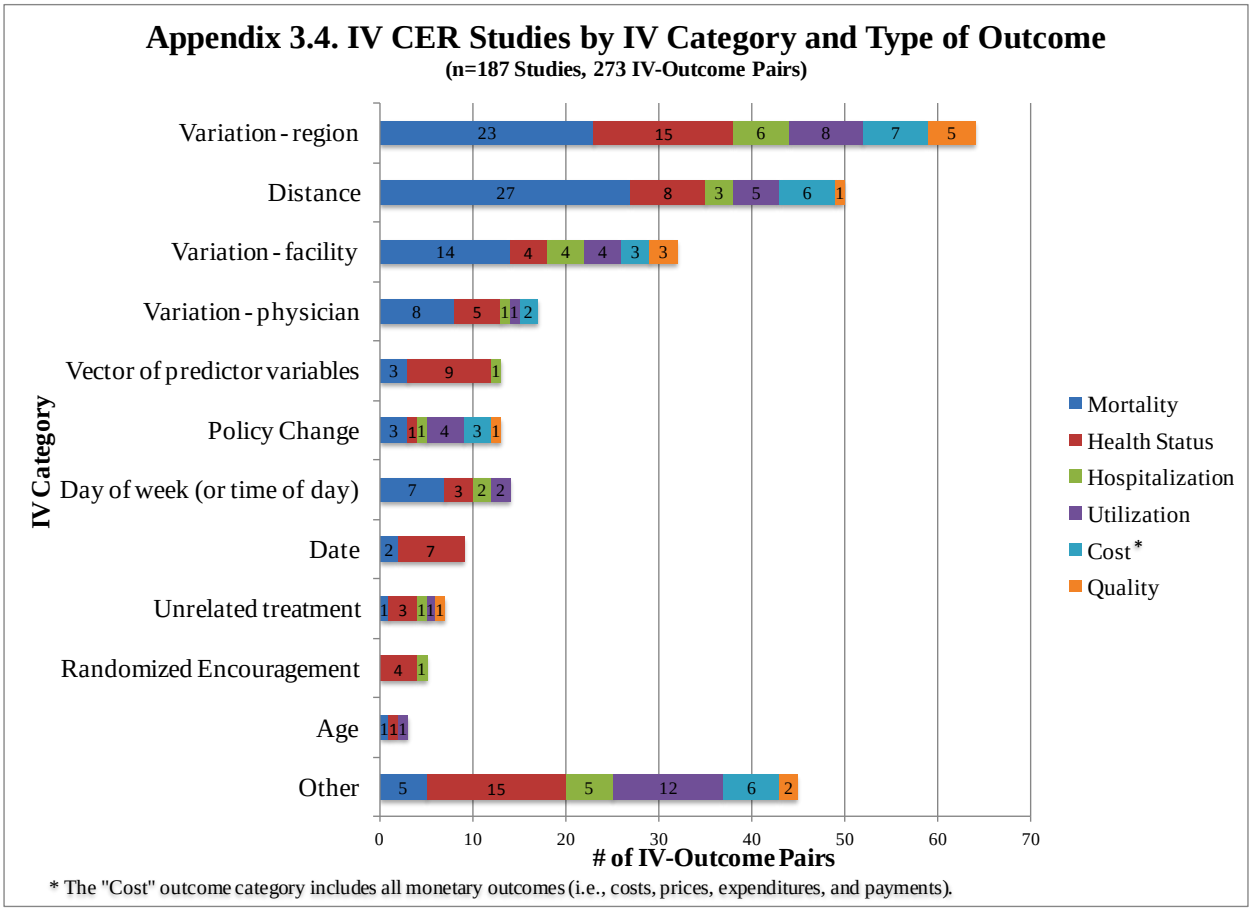
1. We searched for studies that included *both* the IV and the outcome to identify other covariates that are potential confounders.
2. We also performed a two-step search strategy, in which we first searched for evidence of variables that are correlated with the IV and then performed another search to determine whether these variables are also correlated with the outcome, and vice versa.
3. We also identified potential confounders based on our subject matter knowledge and conducted searches to find supporting evidence.
4. Variables that we theorized are related to the IV but for which we do not have empirical evidence to support that the association exists were also identified.

APPENDIX 3.3: DATABASE OF ALL IV CER STUDIES (n=187)

See supplementary digital file Excel worksheet: "Appendix 3"

Note: The lack of consistency in the type of test used to assess IV strength made it difficult to compare IV strength across different studies. IV strength for each study is reported in this database.

APPENDIX 3.4: IV CER STUDIES BY IV CATEGORY AND TYPE OF OUTCOME



APPENDIX 3.5: LIST OF REFERENCES FOR ALL STUDIES THAT PROVIDED EVIDENCE OF IV-OUTCOME CONFOUNDING

See supplementary digital file Excel worksheet: "Appendix 5"

APPENDIX 3.6: CONTROL FOR MAJOR CONFOUNDERS

See supplementary digital file Excel worksheet: "Appendix 6"

APPENDICES 3.7-3.10: DIRECTION OF BIAS INTRODUCED BY CONFOUNDERS

See supplementary digital file Excel worksheet: "Appendix 7" – "Appendix 10"

APPENDIX 3.11: EXAMPLE: CALCULATION OF SIZE AND DIRECTION OF BIAS INTRODUCED BY A CONFOUNDER

Many IV CER studies examined the impact of invasive cardiac procedures following acute myocardial infarction (AMI), with mixed results. Using regional variation in cardiac catheterization as an IV, Stukel et al. (2007) found that cardiac catheterization was associated

with a 16.8% reduction in mortality (7-year all cause) in Medicare patients.[1] Although the authors controlled for many potentially important confounders – e.g., race, income, patient co-morbidities and hospital volume – they did not control for urban vs. rural residence. In this appendix, we provide evidence that urban/rural residence is an IV-outcome confounder and demonstrate how this confounder may bias the IV estimate.

Methods

We first searched the literature for evidence that urban/rural residence (the confounder) is associated with regional variation (the IV) and with mortality (the outcome). We recorded the size and direction of these relationships.

We then estimated the bias introduced by the IV-outcome confounder. The asymptotic bias of the IV estimator can be obtained from a simple equation of the coefficients of three relationships:

Equation 1. $$Bias\left(\hat{a}_{IV}\right) = a_2 \frac{E[U \mid Z=1] - E[U \mid Z=0]}{E[X \mid Z=1] - E[X \mid Z=0]}$$

Where α_2 is the difference in risk of the outcome by level of the confounder, E[U|Z=1] – E[U|Z=0] is the difference in prevalence of the confounder by level of the IV, and E[X|Z=1] – E[X|Z=0] is the difference in prevalence of the treatment by level of the IV. See Brookhart et al. (2007) for a more detailed explanation.[2]

We performed sensitivity analyses with different estimates of the confounder-IV, confounder-outcome, and IV-treatment relationships in order to demonstrate how different sizes and directions of these relationships influence the bias estimate.

Results

We found evidence that urban patients are more likely to live in high cardiac catheterization regions (i.e., assigned to "treatment" via the IV) than patients living in rural areas [see Appendix 3.11 Table 1].[3] In a study using the same Medicare population as Stukel et al. (2007) (the 1994-1995 cohort of the Cooperative Cardiovascular Project), [1] we found evidence that patients treated at urban hospitals have a lower risk of mortality compared to patients in small remote rural hospitals, likely due to decreased use of recommended treatments in rural areas.[4] Since urban patients are more likely to be assigned to the treatment group and less likely to die for reasons other than the treatment of interest, the IV overestimates the true effect of cardiac catheterization [Analysis #1 in Appendix 3.11 Table 1].

There is a smaller mortality difference, and therefore less bias, when comparing urban and large rural hospitals [Analysis #2]. The large differences in urban/rural cardiac catheterization rates, which seem plausible in the early stages of the adoption of a technology, may have reduced over time – this would also decrease the estimate of bias [Analysis #3]. Conversely, the size of the bias is inversely proportional to the association between the IV and the treatment – a weaker instrument will inflate the bias estimate [Analysis #4].

It is also plausible that, in some regions of the US, urban patients have a higher risk of mortality than rural patients and that the IV analysis is actually underestimating the impact of cardiac

catheterization [Analysis #5]. See "Sources of bias example" below for a more detailed explanation of the confounder-IV and confounder-outcome relationships used in this example.

Conclusion

This example demonstrates how the degree of bias is highly dependent on the direction and size of the confounder-IV and confounder-outcome relationships and the strength of the instrument. A confounded IV can lead to overestimation, underestimation or complete reversal of the true treatment effect and a "weak" IV will inflate any residual bias.

Limitations

This analysis is meant to be an example of how to calculate and interpret bias of an IV estimate. The estimates in Appendix 3.11 Table 1 should not be interpreted as the actual bias for Stukel et al. (2007).[1] In order to calculate the actual bias for Stukel et al. (2007), [1] one would need to measure the confounder-outcome and confounder-IV relationships in the study population, while controlling for the other variables in the study. Also, since we analyze the impact of just one IV-outcome confounder we did not adjust for other possible confounders.

Finally, the fact that rural hospitals have been found (in an independent analysis) to have higher mortality does not necessarily imply that rurality is an IV-outcome confounder. It could be argued that the effect of urban/rural residence is mediated through less use of catheterization (i.e., mortality is higher in rural areas because catheterization is less common), in which case the IV analysis is not invalid. However, evidence that patients in rural areas have worse health[5] and receive poorer quality of care (e.g., less likely to receive life-saving aspirin and thrombolytic therapy)[4,6] suggests that mortality is higher for reasons other than just lack of invasive cardiac procedures.

Appendix 3.11 Table 1: Bias Analysis Example

Patient population: AMI Medicare patients
Treatment = cardiac catheterization
Outcome = improved survival (i.e., reduction in mortality)
IV = regional variation in cardiac catheterization rates (reference group = low rate)
Confounder = urban/rural residence (reference group = rural)

Sensitivity Analyses	Confounder-IV Relationship	Confounder-Outcome Relationship	IV-treatment relationship	Bias Estimate (Equation 1)	Effect Estimate (IV estimate – bias)	Interpretation (of IV estimate of actual study)
Actual Study	-	-	22% [a]	-	**IV Estimate = 16.8%** [a]	
Analysis 1 – base case	46% [b]	7%[c]	22%	15%	**2%**	**Overestimate**
Analysis 2 – varied outcome-confounder relationship	46%	**3%** [c]	22%	6%	**11%**	**Overestimate**
Analysis 3 – varied IV-confounder relationship	**23%** [d]	7%	22%	7%	**9%**	**Overestimate**
Analysis 4 – varied IV-treatment relationship	46%	7%	**11%** [d]	29%	**-12%**	**Reverse effect**
Analysis 5 - opposite outcome-confounder relationship	46%	**-10%** [e]	22%	-21%	**38%**	**Underestimate**

Note: Bold numbers in Analyses 2-5 indicate variation from base case (Analysis 1).

Sources for bias example:

(a) 22%: The IV was predictive of catheterization: 65.0% vs. 42.8% of AMI patients in high vs. low use regions received cardiac catheterization (i.e., "strength" of the instrument is 22.2%). [Source: Stukel et al., 2007[1]]

(b) 46%: To obtain an estimate of urban/rural differences by regional rates of cardiac catheterization, we extrapolated from an earlier IV CER study that used distance to cardiac catheterization hospital as the IV, assuming that the patients who live near a cardiac catheterization hospital would also be classified as living in a relatively high utilization rate region. Patients in high cardiac catheterization rate regions were more likely to live in an urban area than patients in a low rate region (52.4%-6.5%=45.9%). [Source: McClellan et al., 1994[3]]

(c) 7%; 3%: Patients in rural hospitals had higher adjusted 30-day post-AMI all-cause mortality than those in urban hospitals (odds ratio for large rural 1.14 [1.10 to 1.18], small rural 1.24 [1.20 to 1.29], and remote small rural 1.32 [1.23 to 1.41]. Patients treated in urban vs. remote small rural (Analysis 1) and large rural (Analysis 2) had a 7% and 3% reduction in mortality, respectively. [Source: Baldwin et al., 2004[4]]

(d) No source. We halved confounder-IV (Analysis 3) and IV-treatment (Analysis 4) relationships for sensitivity analysis.

(e) Murray et al. (2006) demonstrated that urban/rural differences in mortality depend on the region of the country – in some regions, urban populations have lower mortality than rural populations.[7] In addition to race and socioeconomic reasons, there are multiple reasons why urban AMI patients could be sicker, and therefore more likely to die, than rural patients. Over 40% of Medicare patients are transferred out of their admitting hospital,[8] but Stukel et al. (2007)[1] did not take into account transfer status of the patients. Studies on other medical conditions found that transferred patients are more likely to be from rural areas[9] and sicker[10,11] – this leaves a relatively healthier population in rural hospitals. Similarly, patients who live in rural areas have a longer travel time to the hospital.[12,13] For life-threatening illnesses, such as AMI, patients who have to travel longer distances are less likely to arrive at the hospital (i.e., they die en route). A person with a similarly severe illness in an urban area would have made it to the hospital and been included in the study population. Again, this results in a relatively healthier patient population in the rural hospitals.

References for bias example:

[1] Stukel TA, Fisher ES, Wennberg DE, et al. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA*. 2007;297(3):278–285.

[2] Brookhart MA, Schneeweiss S. Preference-based instrumental variable methods for the estimation of treatment effects: assessing validity and interpreting results. *Int J Biostat*. 2007;3(1):14.

[3] McClellan M, McNeil BJ, Newhouse JP. Does more intensive treatment of acute myocardial infarction in the elderly reduce mortality? Analysis using instrumental variables. *JAMA.* 1994;272(11):859–866.

[4] Baldwin LM, MacLehose RF, Hart LG, Beaver SK, Every N, Chan L. Quality of care for acute myocardial infarction in rural and urban US hospitals. *J Rural Health.* 2004;20(2):99-108.

[5] Danaei G, Rimm EB, Oza S, et al. The promise of prevention: the effects of four preventable risk factors on national life expectancy and life expectancy disparities by race and county in the United States. *PLoS Med.* 2010;7(3):e1000248.

[6] Willison DJ, Soumerai SB, Palmer RH. Association of physician and hospital volume with use of aspirin and reperfusion therapy in acute myocardial infarction. *Med Care*. 2000;38(11):1092-1102.

[7] Murray CJL, Kulkarni SC, Michaud C, et al. Eight Americas: investigating mortality disparities across races, counties, and race-counties in the United States. *PLoS Med.* 2006;3(9):e260.

[8] Iwashyna TJ, Kahn JM, Hayward RA, Nallamothu BK. Interhospital transfers among Medicare beneficiaries admitted for acute myocardial infarction at nonrevascularization hospitals. *Circ Cardiovasc Qual Outcomes*. 2010;3(5):468–475.

[9] Maybury RS, Chang DC, Freischlag JA. Rural hospitals face a higher burden of ruptured abdominal aortic aneurysm and are more likely to transfer patients for emergent repair. *J Am Coll Surg*. 2011;212(6):1061-7.

[10] Culica D, Aday LA, Rohrer JE. Regionalized trauma care system in Texas: implications for redesigning trauma systems. *Med Sci Monit.* 2007;13(5):SR9-18.

[11] Durairaj L, Will JG, Torner JC, Doebbeling BN. Prognostic factors for mortality following interhospital transfers to the medical intensive care unit of a tertiary referral center. *Crit. Care Med.* 2003;31(7):1981–1986.

[12] Abrams TE, Vaughan-Sarrazin M, Fan VS, Kaboli PJ. Geographic isolation and the risk for chronic obstructive pulmonary disease-related mortality: a cohort study. *Ann. Intern. Med.* 2011;155(2):80–86.

[13] Khan JA, Casper M, Asimos AW, et al. Geographic and sociodemographic disparities in drive times to Joint Commission-certified primary stroke centers in North Carolina, South Carolina, and Georgia. *Prev Chronic Dis*. 2011;8(4):A79.